PB 189 363

GUIDELINES TO RADIOLOGICAL HEALTH

Bureau of Radiological Health
Rockville, Maryland

September 1968

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ENVIRONMENTAL HEALTH SERIES
Radiological Health

GUIDELINES TO RADIOLOGICAL HEALTH

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Consumer Protection and Environmental Health Service

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GUIDELINES TO RADIOLOGICAL HEALTH

Lectures presented at the International Conference at McGill University, Montreal, Canada, August 1967, in collaboration with the U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Radiological Health, and the Department of National Health and Welfare, Radiation Protection Division, Ottawa, Canada.

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Consumer Protection and Environmental Health Service
Environmental Control Administration
Bureau of Radiological Health
Rockville, Maryland 20852

Library of Congress catalog card number 68-62513

Public Health Service Publication No. 999-RH-33

September 1968

U.S. GOVERNMENT PRINTING OFFICE, WASHINGTON : 1968

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ABSTRACT

Under the sponsorship of the U.S. Department of Health, Education, and Welfare, Public Health Service, National Center for Radiological Health, and the Department of National Health and Welfare, Radiation Protection Division, Ottawa, Canada, the International Conference on "Guidelines to Radiological Health" was held at McGill University, Montreal, Quebec, Canada, August 1967, to discuss radiological health problems, as presented by a group of experts. Speakers from the United States, Canada, Great Britain, and Japan presented papers on three major topics: Radiation Injury, Preventive Measures, and Sources of Radiation and Epidemiology, and included the fields of diagnostic and therepeutic radiation, industrial exposure to radiation, changes induced by irradiation of nutritional elements, and radioecological concentration processes.

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MECHANISM OF RADIATION INJURY

John R. Totter

Injury from high-energy radiation was discovered almost as soon as that type of radiation itself was discovered. Unfortunately, the subsequent development of knowledge concerning the mechanism of injury to biological material did not follow so rapid and fruitful a course as did the development of knowledge about the physics of radiation. Medical personnel and others who worked with x rays quickly found ways to protect themselves from overexposures and gradually learned more about the insidious effects of continued small doses. Those working with concentrated sources of radioactive elements took somewhat longer to realize the dangers associated with intake of small quantities of these substances; nevertheless, by the end of the third decade after the discovery of radium, the nature of the danger was well understood by many even though the mechanisms of injury were still obscure.

For purposes of a general introduction to the subject, it is best to ignore the chronology of discovery and try to present an overall view of what is now known about the mechanism of radiation injury, starting at the molecular level and proceeding to cellular and organ effects.

At present, the best understood radiation injury is that brought about in bacterial cells by absorption of ultraviolet light. Most of the molecular change occurs in the thymine of the deoxyribonucleic acid—the genetic material of the cell. Adjacent thymine moieties link together to form "thymine dimers" as a result of the chemical changes following absorption of energy from the irradiation in the pyrimidine bases. Perhaps some energy is transferred from the purine bases—adenine and guanine—and from the other major pyrimidine base—cytosive. Some dimerization may also occur with the other bases but the most studied case is that of the thymine. The change can in some cases be reversed by irradiation with more energetic light of the proper wavelength, or through the action of special enzymes that can excise the altered nucleotides and replace them with unchanged thymidylic acid; thus, recovery can occur "spontaneously." Bacteria, which do not contain the necessary recovery enzymes, cannot undergo a complete DNA replication cycle if the thymine dimers persist, and hence are unable to reproduce—in effect they are "dead." Recovery in bacteria has been found to be under genetic control and the genes responsible may be introduced into strains not having them by proper mating.

Injuries from higher energy radiations are superficially similar to ultraviolet light injuries in that the most significant changes occur in the genetic apparatus of the cell. The results differ from those of ultraviolet damage in that the higher energy radiations are randomly absorbed rather than specifically absorbed. Unlike the DNA of bacteria, DNA of higher organisms is associated with nucleoprotein that may offer protection or provide molecules with which to crosslink under the influence of radiation; thus, it would not be expected that the major change would be exhibited in the appearance of a single type of lesion in one of the DNA bases. Rather, one would expect that many types of changes would be found. Some of these resemble ultraviolet damage in that recovery is possible and there is much current research on the mechanism of recovery from the effects of ionizing radiation. Recovery in DNA synthesis may occur in rare instances without complete recovery in its function.

It is now believed that a major component of the difference in susceptibility to killing by ionizing radiation, especially in the animal kingdom, may reside in a differing ability to bring about repairs to damaged DNA at the subcellular level. This appears to differ from the situation in higher plants where the sensitivity to killing by gamma rays is relatively closely correlated with the chromosome volume. Repairs of radiation injury in this case may be a minor factor, or may be similar in extent in almost all of the plants so far examined for their susceptibility.

As would be expected, injury to the cellular genetic material, which must be replicated without change or with only minor changes for cell multipication to occur, is exhibited in the multicellular organism by failure of an organ to maintain itself. In higher animals, the organs most dependent upon cell renewal for their proper functioning are the blood cellular elements, the lining of the intestinal tract, and the skin. These organs are necessary for continued viability, and death results from failure to regain their functional capacity. In some cases it has been possible by transplantation to replace stem cells, and thus tide the animal over a critical period. Other organs with little dependence on a rapidly continuing cell proliferation do not exhibit overt damage but nevertheless sustain similar injury. Not being able to remove injured cells by rapid replacement of those that might suffer mitotic death in tissues, with rapid cell turnover, these organs must undergo only a very slow repair. The animal suffering whole-body irradiation, which has been able to repair its hemopoietic, intestinal, and dermal tissues seemingly completely; nevertheless, still carries in its other organs and tissues a less manifest and less specific load of cell injury which we can as yet best recognize as a shortening in life span.

RADIOSENSITIVITY OF CELLS

Gordon F. Whitmore

We have been concerned for some time with attempts to determine the nature of the radiation-induced lesions responsible for the death of mammalian cells in tissue culture, with the assumption that in all probability, many of these same lesions would be responsible for the death of mammalian cells in in vivo situations. In particular, we have recently been interested in the variation in sensitivity that can be produced by changing the environment of the cell or its physiological condition either immediately before or after irradiation, and we have also been interested in the nature of the repair processes that take place following irradiation.

I think by now most of you will be familiar with the fact that mammalian cell survival curves are characterized at low doses by a shoulder region where a given increment of dose is much less effective than the same increment of dose given immediately following the previous dose of radiation. The presence of this shoulder suggests that cells are accumulating some form of sublethal damage, and this suggested to Elkind the possibility that under certain circumstances the cell might be capable of repairing some of this sublethal damage (*1–3*). It occurred to Elkind that the easiest way to look for such repair would be to subject the cell to two doses of radiation separated by various intervals of time to determine how the survival level varied with the time interval between the doses. The general shape of the recovery curve which he found for Chinese hamster cells is illustrated in figure 1 which shows a typical two-dose recovery curve obtained with L-cells given an initial exposure to 700 rads, and, after various time intervals, a second exposure to 500 rads. The curve is complex in shape and we are now convinced on the basis of evidence, which I will not present, that this recovery curve is the result of at least two processes. The initial rise in the survival level is due to the fact that the cells are capable of repairing some forms of radiation damage. The secondary minimum and the final rise in survival are due to the fact that the cells, which survive the first dose of radiation, are progressing through the cell cycle, and as they do they pass through regions of various sensitivities to radiation.

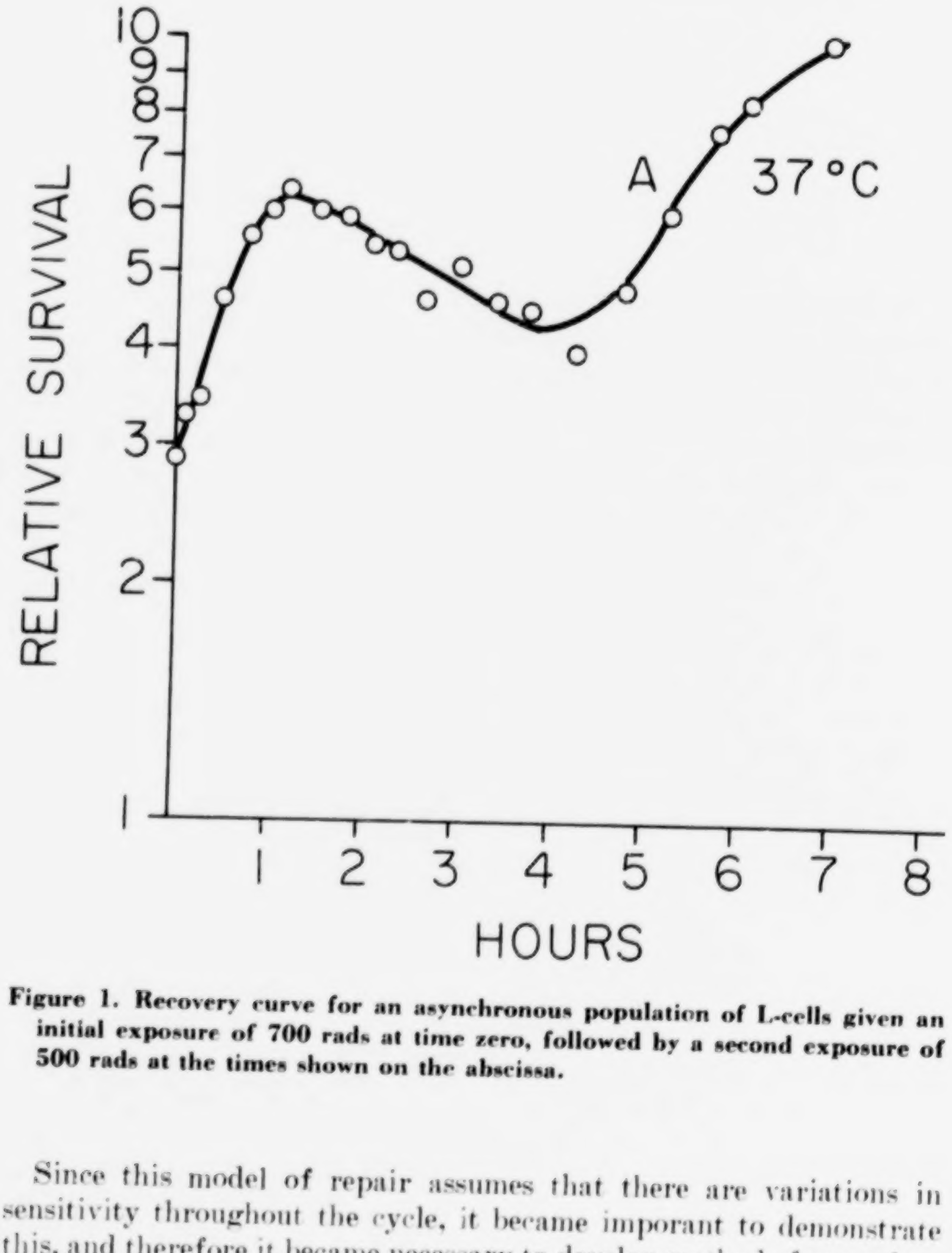

Figure 1. Recovery curve for an asynchronous population of L-cells given an initial exposure of 700 rads at time zero, followed by a second exposure of 500 rads at the times shown on the abscissa.

Since this model of repair assumes that there are variations in sensitivity throughout the cycle, it became imporant to demonstrate this, and therefore it became necessary to develop methods for producing synchronized populations. Several such methods have been developed (*4–6*) but I will only deal with the method that has been used in our own experiments (*7*) (illustrated in fig. 2). This figure shows a normal cell cy le with an S phase, when all the DNA of the

cell is synthesized, and three other phases during which there is no DNA synthesis taking place. If an asynchronous population containing cells in all phases of the cell cycle is exposed to a high concentration of high specific activity tritiated thymidine, then those cells, which are synthesizing DNA, will rapidly incorporate the label and be killed by the radioactive decay. If the labeled material is left in the population long enough, G_2, M, and G_1 will ultimately all be drained of viable cells; however, the uptake of the radioactive material can be stopped at any time by the addition of unlabeled thymidine. If this is done after a 6-hour exposure in our cell system, then we are left with a narrow window of viable cells late in the G_1 phase, and these constitute a synchronized population.

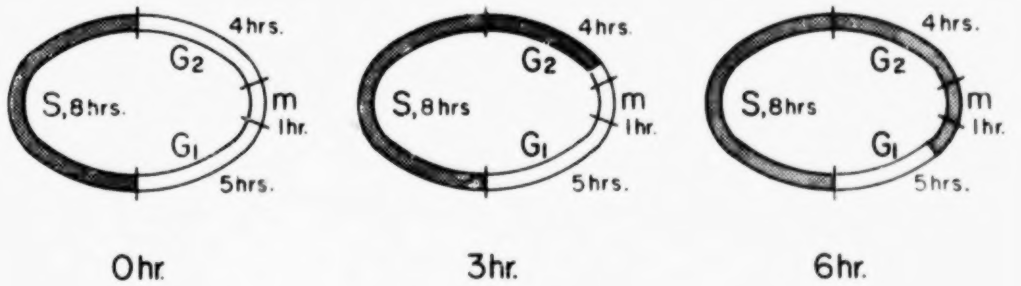

Figure 2. Schematic representation of the fraction of mouse L-cells killed (blackened area) as a function of time of exposure to high-specific activity tritiated thymidine.

With a synchronized population, it is possible to measure variations in radiation sensitivity around the cell cycle. Figure 3 shows survival curves of L-cell populations irradiated in G_1, S, and G_2. For our cell line, cells in G_1 and G_2 phase are relatively insensitive while cells in the S phase are relatively sensitive. This variation is illustrated in another way in figure 4, which shows the fraction of cells in each phase of the cell cycle that would survive a dose of 1,200 rads. Once again, you can see that the cells in the late S phase are the most sensitive, whereas cells in the G_1 and G_2 are relatively resistant.

The data presented above indicate that cell sensitivity does vary around the cell cycle and provide support for at least part of the model for recovery from radiation damage. The next problem was to demonstrate the existence of repair phenomena and to attempt to determine, if possible, the nature of this repair phenomena; that is, the nature of the biochemical processes that was involved. Without presenting the evidence I will just state that cells in all parts of the cell

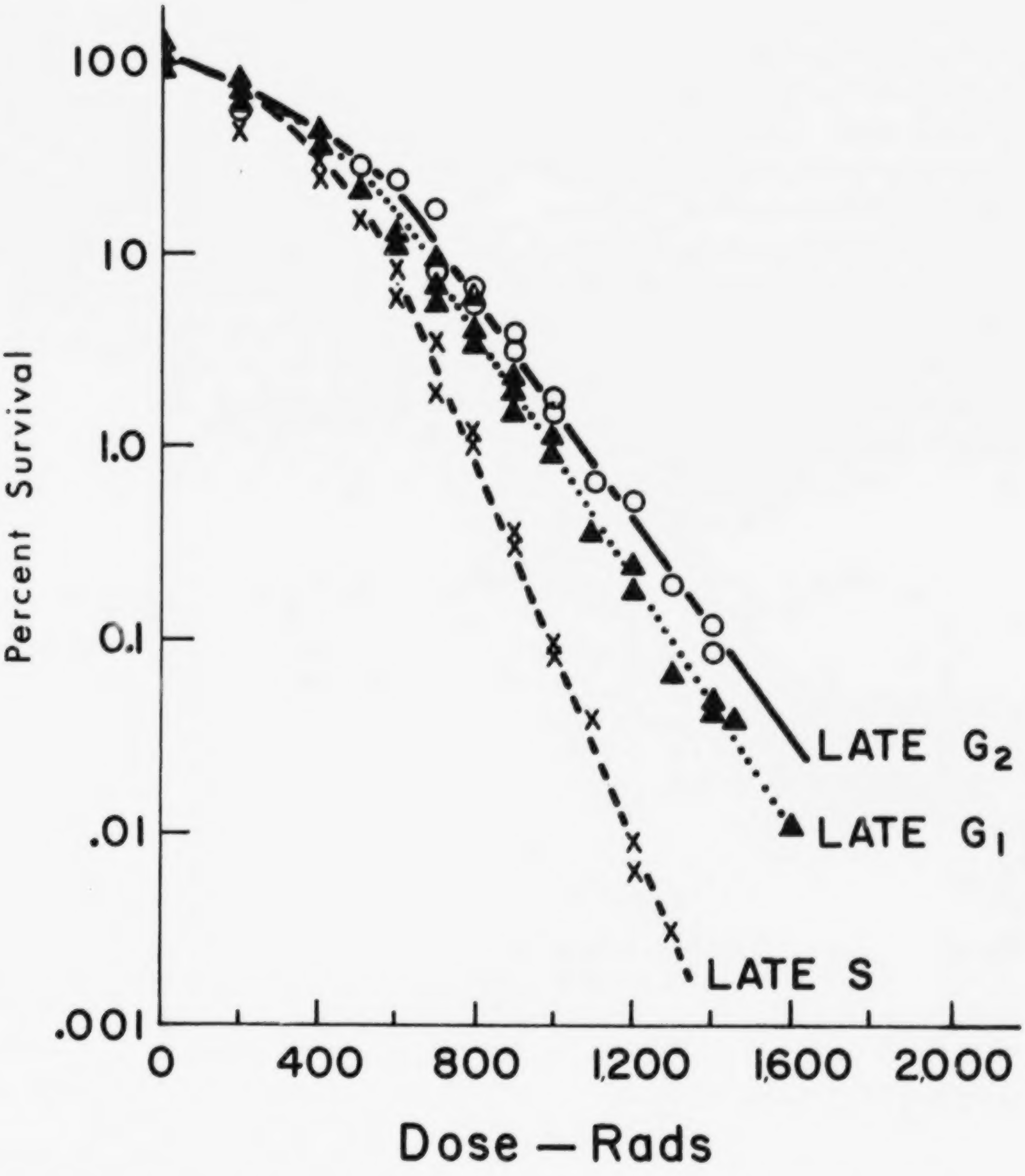

Figure 3. Survival curves for mouse L-cells irradiated in G_1, S, and G_2.

cycle can demonstrate recovery; that this recovery is apparently independent (at least at early times) of DNA, RNA, and protein synthesis and can occur in the presence of inhibitors of the synthesis of all of these macromolecules. Finally, repair can take place at low temperatures and under conditions where we know that no DNA, RNA, or protein synthesis is taking place. This evidence would suggest that we are dealing with a physical-chemical decay process whereby lesions are formed and then decay by some form of physical-chemical process.

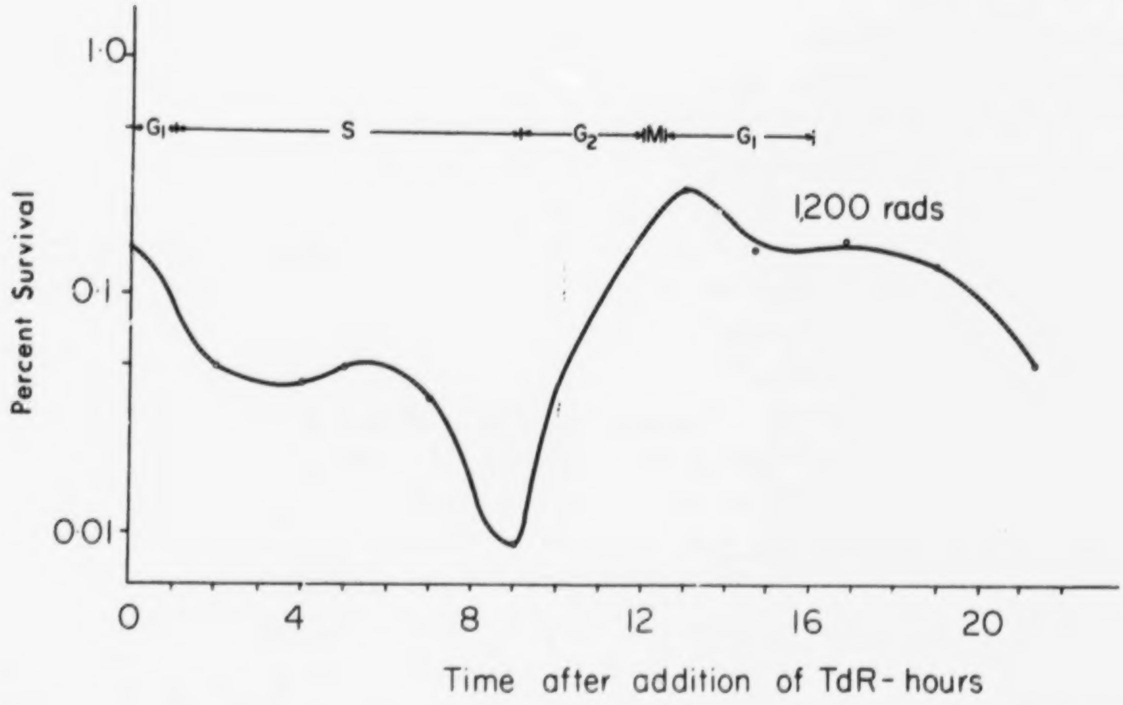

Figure 4. The survival curve of mouse L-cells exposed to a single dose at 1,200 rads at various times in the cell cycle.

Most of the recovery experiments carried out by Elkind (*1–3*, *8–11*) and his associates and others (*12*), and many of the experiments carried out in our own laboratory have been concerned with two-dose experiments of the type—x ray, time interval, second dose of x rays. These experiments appear to have been based on the classical concept of multitarget or multihit type of inactivation; that is, it was assumed that a cell would only be inactivated when either a number of targets within the cell had been inactivated or when the single target within the cell had been struck by a number of inactivating events. For this reason these lesions were referred to as sublethal because every sublethal lesion required the addition of further radiation in order for it to become lethal. Another possible explanation for this type of data is that there is within the cell what we have called a potentially lethal type of lesion (a lesion that has the potential of killing the cell), and its probability of killing the cell is dependent on the physiological condition of the cell at the time of irradiation and perhaps immediately following irradiation. We, therefore, have attempted to determine whether such potentially lethal lesions existed within the cell, and the principal part of my talk today will be concerned with attempts to demonstrate the existence of this potentially lethal type of lesion and some of the conditions that can be used to alter the probability that such a lesion will lead to cell death.

Before describing these experiments, perhaps we could take a minute to discuss in more detail the model upon which they are based. The model assumes that radiation produced a class of potentially lethal lesions within the cell and that following the induction of these lesions, they may either be repaired (in which case the cells survive) or they may be incorporated into the cell's biochemical mechanisms (in which case the cell dies or at least has an increased probability of dying). The difference between this hypothesis and the hypothesis of sublethal lesions on which the two-dose fractionation experiments were based is not completely obvious. The model, which led to the two-dose fractionation experiments, is based on the idea that there is a class of radiation that is not lethal per se but requires more radiation in order to become lethal. This model, as we mentioned, is consistent with either the multihit or multitarget type of inactivation scheme. The model on which we are now working is that of the potentially lethal lesion that may become lethal even in the absence of further radiation. We have not ruled out the possibility that further radiation could alter the probabilities of lethality—either by damaging a repair process or by adding more potentially lethal lesions with which the original lesion might interact. If there are potentially lethal lesions of the type we have described, and if they are relatively long-lived, then this opens up the possibility of demonstrating their existence by changing conditions following irradiation in such a way as to either foster the repair or the incorporation of the lesions following a single dose of radiation. In an attempt to see to what extent this might be possible, we have made use of low temperature and other post-radiation treatments in an attempt to alter the radiation sensitivity. Most of the experiments I will describe today will be based only on low temperatures since they are technically better experiments and our control experiment suggests that these and certain chemical agents are both protecting against the same type of lesion. A combination of the two gives no more protection than either one alone.

Figure 5 shows four survival curves—the most sensitive is for cells grown, irradiated, and maintained at 37° C. after irradiation. The least sensitive is for cells cooled to 5° C. for 1 hour following irradiation. The intermediate curves are for populations irradiated at 37° C. and immediately cooled to 5° C., and for a population irradiated at 5° C. and immediately warmed to 37° C. It is obvious that post-irradiation alterations in temperature can, therefore, affect the survival level.

Up to this point, the experiments we have been describing have been carried out on asynchronous populations and then we asked whether this type of phenomenon could be demonstrated in all parts of the cell

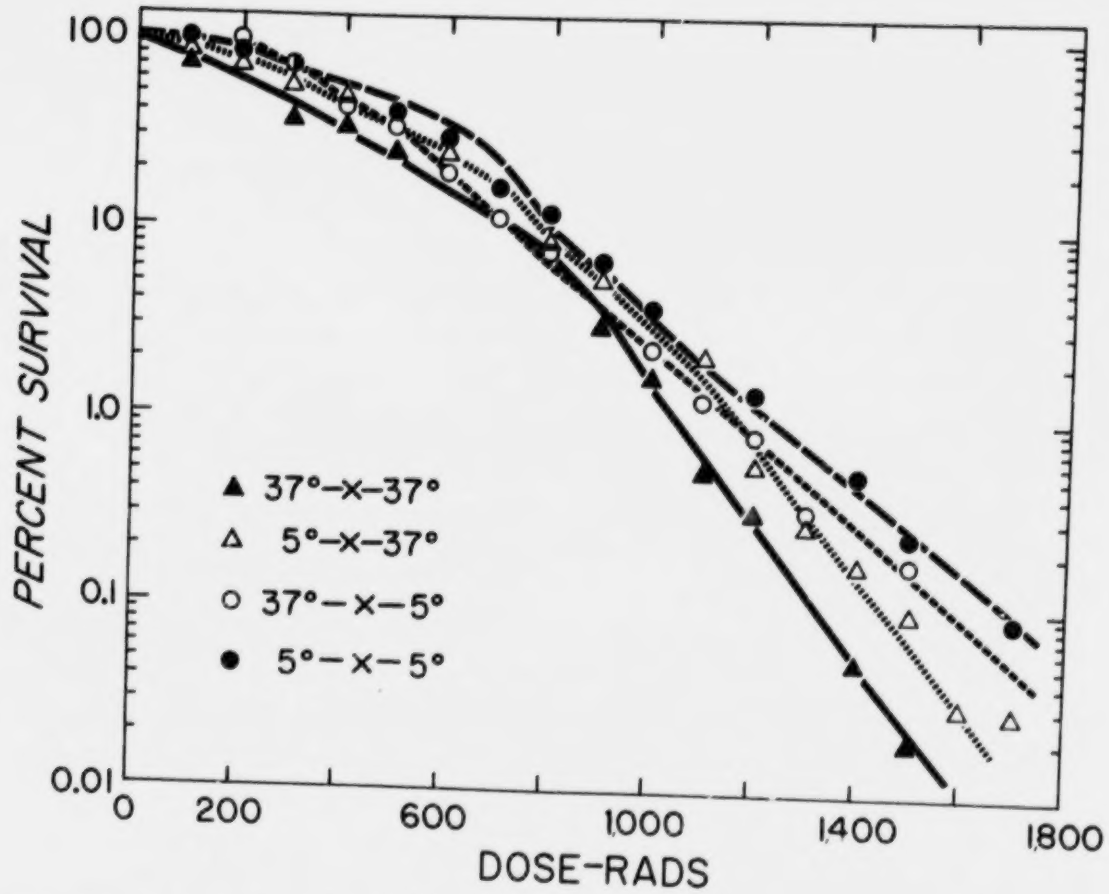

Figure 5. Survival curves for L-cells irradiated at 37° C. and plated immediately; for cells cooled to 5° C., irradiated and kept at 5° C. for 1 hour prior to plating; for cells cooled to 5° C., irradiated and immediately plated at 37° C.; and for cells irradiated at 37° C. and then cooled to 5° C. for 1 hour prior to plating.

cycle. In order to answer this question several experiments were carried out. Figure 6 shows the results of the first of these. In this experiment, four synchronized populations—one in G_1, one in early S, one in late S, and one in G_2—were irradiated either at 37° C. or at 5° C., and complete survival curves determined. It was obvious that there is protection in all parts of the cycle but that it is greatest in the S phase.

Having demonstrated the phenomenon of cold protection in all parts of the cell cycle, we then asked at what rates damage was repaired in all parts of the cell cycle, or, if you like, we asked how long does the cell have the ability to either repair or incorporate damage. The results of this experiment are shown in figure 7. At first glance this may seem rather complicated but the idea is relatively simple if we devote our attention initially to one of the panels. This experiment was carried out with four synchronized populations, and each one was divided into two parts, one part was cooled to 5° C. for 1 hour before irradiation and the other was left at 37° C. After irradiation with a dose of 1,000 rads, aliquots were removed from the population at various times at

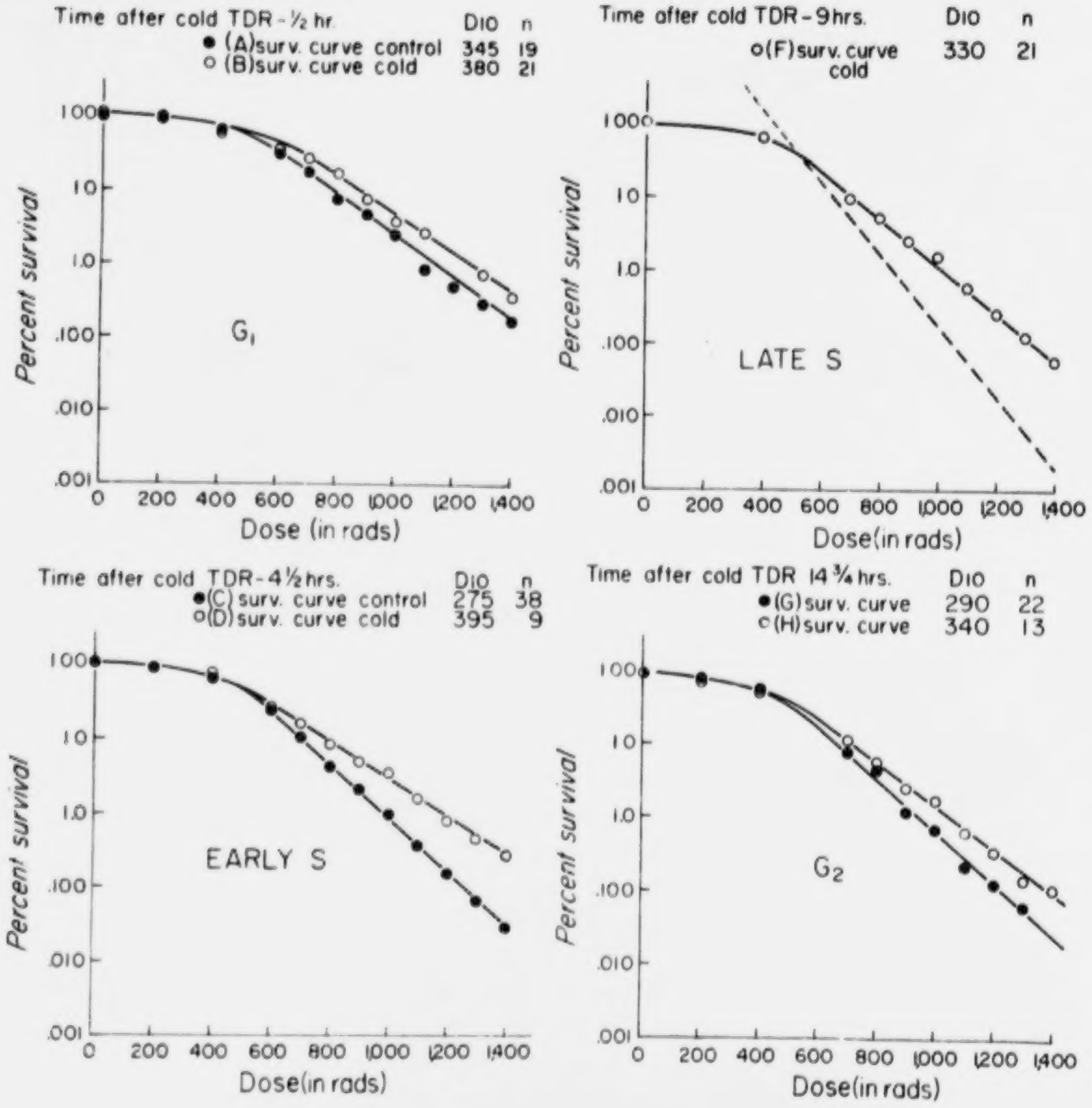

Figure 6. Survival curves for synchronized populations of mouse L-cells in G_1, early S, late S, and G_2, irradiated at either 37° C. or 5° C.

5° C. and incubated at 37° C. before being plated. In the same way at various times aliquots were removed from the population irradiated at 37° C. and cooled to 5° C. for 2 hours. If we now look at the data for the population irradiated in the early S phase, we see that when cells are irradiated at 37° C. and then shifted to low temperatures immediately after irradiation, they show a low sensitivity; but as the time interval between irradiation and cooling is increased the survival level drops, and after about 30 minutes following irradiation a transfer to low temperature appears to have little or no effect on the survival level. It is as if all of the damage had been fixed by this time. Conversely, for cells irradiated at 5° C. and immediately shifted to 37° C., the survival is a minimum, but as the time interval between irradiation and warming is increased, the survival level increases and reaches a

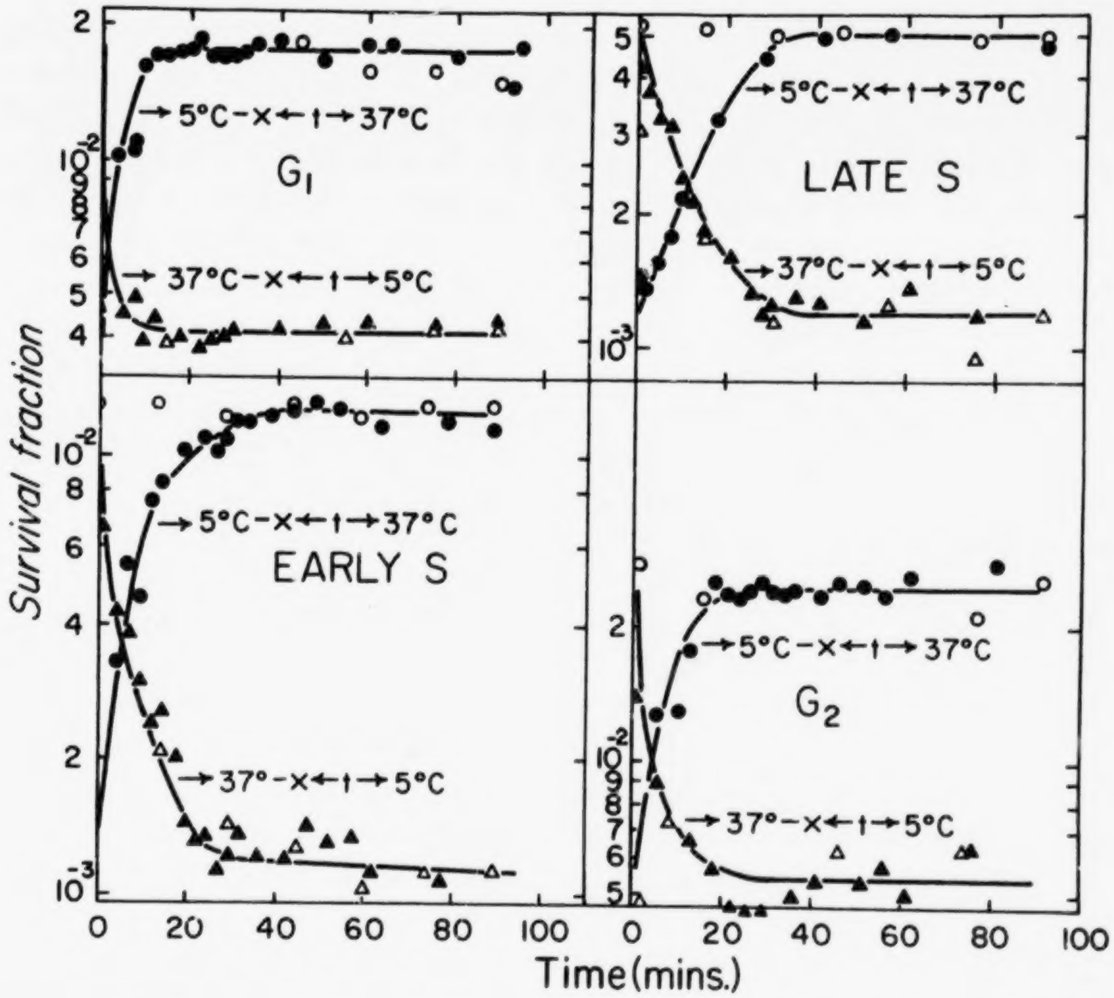

Figure 7. Survival curves showing the rate of fixation and repair of potentially lethal damage for synchronized cell populations.

maximum after about 30 minutes, indicating that the fate of the lesion seems to have been decided in the first 30 minutes following irradiation. If we now compare the results for irradiation in various parts of the cell cycle, we see they all show similar trends, but the amount of protection conferred by post-treatment seems to be a maximum for cells irradiated early in the S phase, and less for cells irradiated in G_1 or G_2. It also appears that late in the S phase it may take longer for the fate of the lesions to be decided.

I think we can assume that low temperature is a very nonspecific inhibitor of cellular metabolism and this prompts the question as to whether the protection offered by low temperatures is a result of a cessation of some particular process or whether it merely reflects the fact that the cells have a reduced metabolic rate or utilization of some particular component that allows it to repair some damage before it is called upon to make use of the structure or system that contains this damage. In other words, we are assuming that the processes responsible for the repair of damage are less responsive to low temperatures than are the remaining processes of the cell. If the protection is not a specific property of low temperatures but merely of a reduced metabolic rate, then other conditions that reduce the cellular metabolic rate might be expected to render the cell less sensitive to radiation. In an attempt to see whether this is so we have irradiated cells both at 5° C. and 37° C. in the logarithmic phase of growth and in the stationary phase, which occurs when cells have overgrown their medium. The results of this experiment are shown in figures 8 and 9. Figure 8 shows the growth curve for the cells used in this experiment. Irradiations were carried out at 37° C. at the times indicated by the letters, A, C, E, and G; and at 5° C. at the times indicated by the letters B, D, F, and H. The resulting survival curves are shown in figure 9. A comparison of the curves at 37° C. indicates that in the stationary phase the cells are less sensitive than in the logarithmic phase. For cells in the logarithmic phase, low temperatures protect, but in the stationary phase the survival curves appear to be independent of the temperature at the time of irradiation.

In summary, I think the experiments presented up to this point have indicated that in addition to any nonrepairable lesions that may be produced by radiation, there is a class of lesions produced that have the potential of becoming lethal or of being repaired. The existence of such a lesion is demanded by the fact that post-irradiation treatments can affect the survival level. This immediately poses the question as to whether the split-dose and post-treatment experiments are in fact measuring the same type of lesion. There is evidence which suggests that they are, but this is certainly not definite as yet.

Up to this point, the inhibitors used in the post-treatment experiments (both cold and the various inhibitors) are extremely nonspecific and really give us very little information as to the nature of the biochemical process involved; however, it appeared that there was some evidence that suggested that RNA synthesis might somehow be involved in determining radiation sensitivity.

First of these was our observation that cells are less sensitive in stationary phase and the biggest change in metabolism between log and stationary phase cells seems to concern RNA synthesis. The second observation came out of some experiments on the effect of phenethyl alcohol on DNA and RNA synthesis. Bruchovsky (*13*) has shown that in the presence of phenethyl alcohol, DNA, RNA, and protein synthesis all came to an essential standstill, but cells left in phenethyl alcohol for periods exceeding 4 to 6 hours would once again begin to synthesize RNA. We had noticed in several experiments with phenethyl

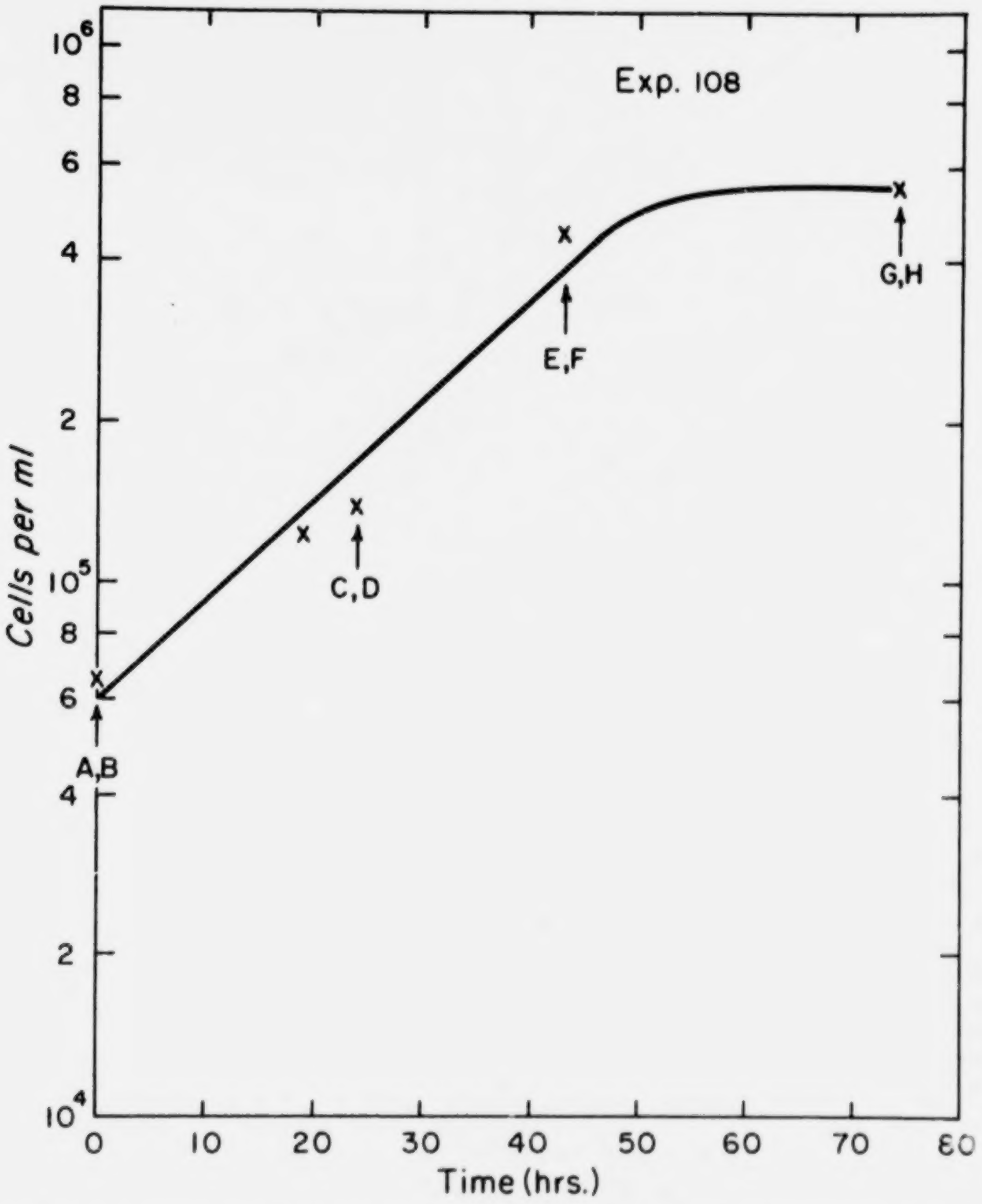

Figure 8. Growth curve of the cell population used for the experiments shown in figure 9.

alcohol that some alteration in radiation sensitivity began to appear about this time.

Further evidence for the involvement of RNA synthesis comes from the same experiment using methotrexate. Methotrexate is an inhibitor that acts in a number of places in the biosynthetic pathways of mammalian cells. The main ones we are concerned with today are the blocking of DNA synthesis because of blockage of thymidylate and purine synthesis and the blocking of RNA synthesis brought on by the lack

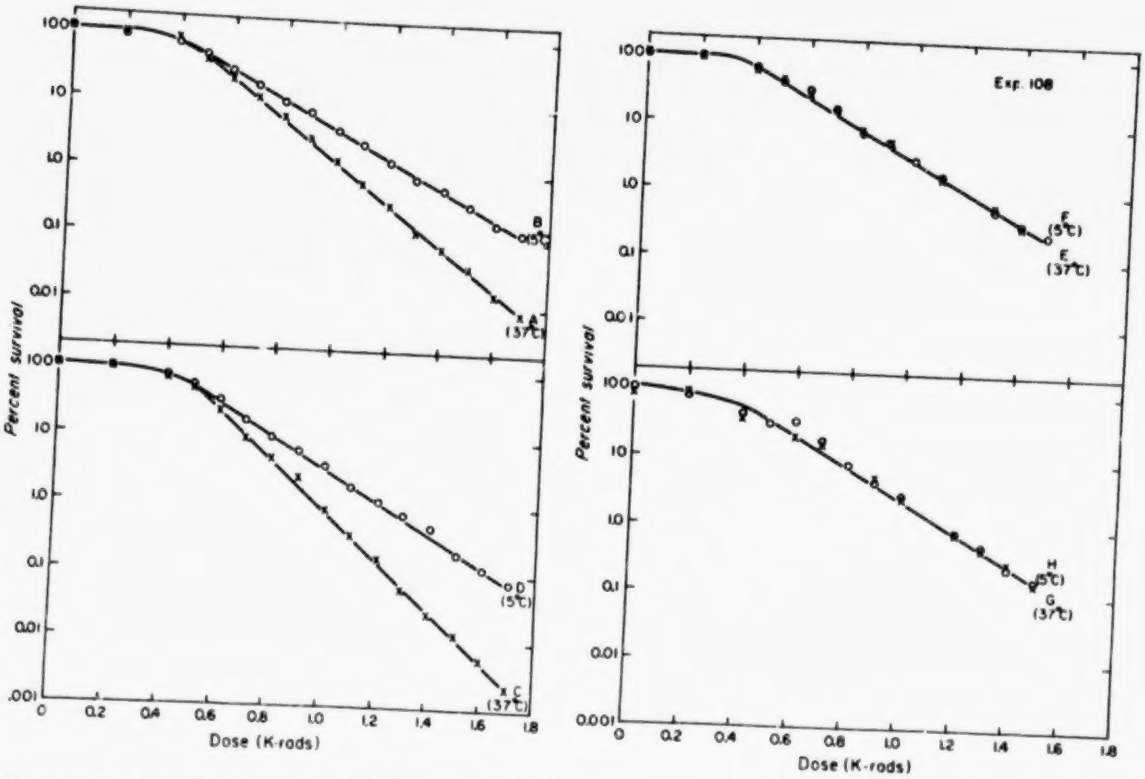

Figure 9. Survival curves for the L-cell populations whose growth curve is shown in figure 8. At each point on the growth curve survival curves were determined at either 5° C. or 37° C.

of purine synthesis. The fact that DNA synthesis is blocked in two respects while RNA is blocked only by a lack of purines synthesis means that it is possible to select a condition that allows RNA synthesis in the absence of DNA synthesis. This possibility seemed to suggest that the compound might be useful in our radiation studies.

Figure 10 shows the effect of methotrexate on cell survival in the absence of radiation at the concentrations we will be using. There is no apparent killing for at least 10 hours; in all of the experiments we will talk about except one, methotrexate was not present for this length of time. In that experiment, adequate control experiments were carried out.

Figure 11 shows the rate of RNA synthesis as measured by uridine uptake as a function of time after the addition of methotrexate. In this figure, curve A is the control population without methotrexate, curve B is for cells in the presence of methotrexate from the time zero, C is the uptake when Leucovorin was added 7 hours after methotrexate, and D is the uptake when deoxyadenosine was added 7 hours after methotrexate to allow RNA synthesis to commence. Since our primary interest will be in situations similar to A and B, we might just empha-

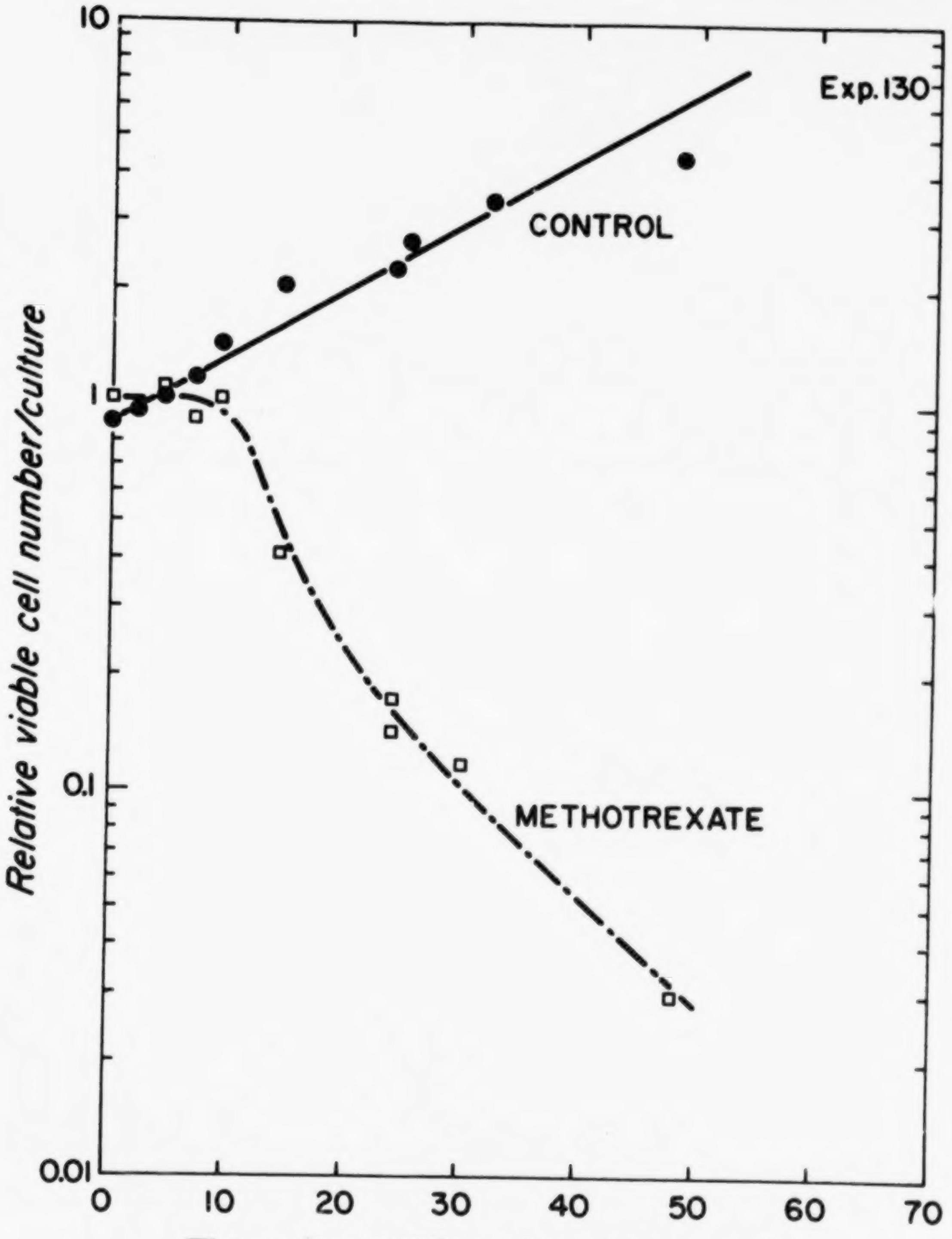

Figure 10. Viable cell determination in a control population and a population exposed to 10^{-6} g/ml of methotrexate for the times shown.

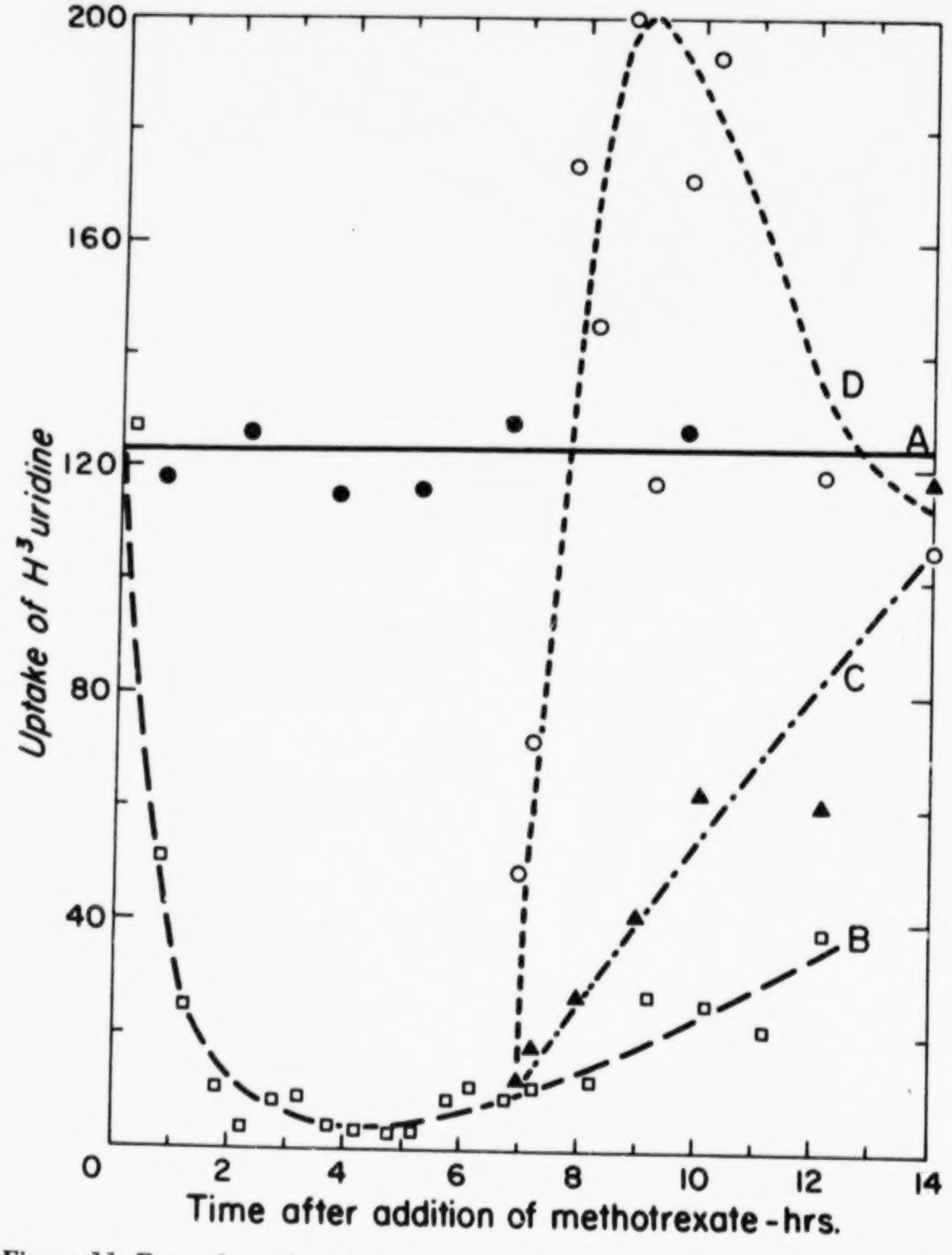

Figure 11. Rate of uptake of tritiated uridine in a control population (A); in a population treated with 10^{-6} g/ml methotrexate (B); and in populations treated with 10^{-6} g/ml methotrexate but given Leucovorin (C) or deoxyadenosine (D) after 6¼ hours.

size that in the presence of methotrexate, RNA synthesis drops to zero at about 4 hours after the addition of the compound. When deoxyadenosine is added 7 hours after, there is a rapid increase in the rate of RNA synthesis, an overshoot when the rate is greater than in the control and then it appears to return to normal.

If radiation sensitivity is correlated with the rate of RNA synthesis and if cells are more sensitive to radiation when RNA is being rapidly synthesized then in an irradiation experiment using a single dose at various times after the addition of methotrexate and its reversing compounds, we should expect to get curve shapes that are almost the mirror images of these curves; that is, the survival should be low when the rate of uptake is high and vice versa. Figure 12 shows the results of such an experiment. In this experiment, the methotrexate was added at time zero and the upper curve shows the survival for cells exposed to 1,000 rads as a function of time. Under these circumstances, the survival reaches a maximum value at about 4 to 5 hours after the addition of the compound, about the same time as the amount of RNA synthesis reaches a minimum and it remains at this level. If Leucovorin is added, however, to the methotrexate-treated cells, then the sensitivity to radiation begins to increase. If the deoxyadenosine is added, then the sensitivity rapidly increases and the cells actually become more sensitive than the control. It will be remembered that about this time, the rate of RNA synthesis also exceeds the rate of synthesis in the control cultures. As a final indication of the radiation response state of these cells treated with methotrexate and methotrexate plus deoxyadenosine, we have measured the survival curves shown in figure 13 for a control population, a population treated with methotrexate for 6¼ hours followed by deoxyadenosine for 5 hours. It is apparent that the methotrexate treated cells have a higher D_0 than the control cells, and the methotrexate plus deoxyadenosine treated cells a lower D_0 than the control population.

This concludes the data I would like to present and now it would appear necessary to try and correlate it into some kind of consistent picture. It seems to me that there is now evidence from both two-dose and single-dose experiments that there are lesions produced in the cell that may or may not be repaired. There is also evidence from studies on the variation of sensitivity around the cycle and from work I have presented that the state of the cells' metabolism has a pronounced bearing on the response to radiation, and this, of course, has obvious ramifications in the treatment of cancer. These observations pose a number of problems. Do the two-dose and single-dose repair experi-

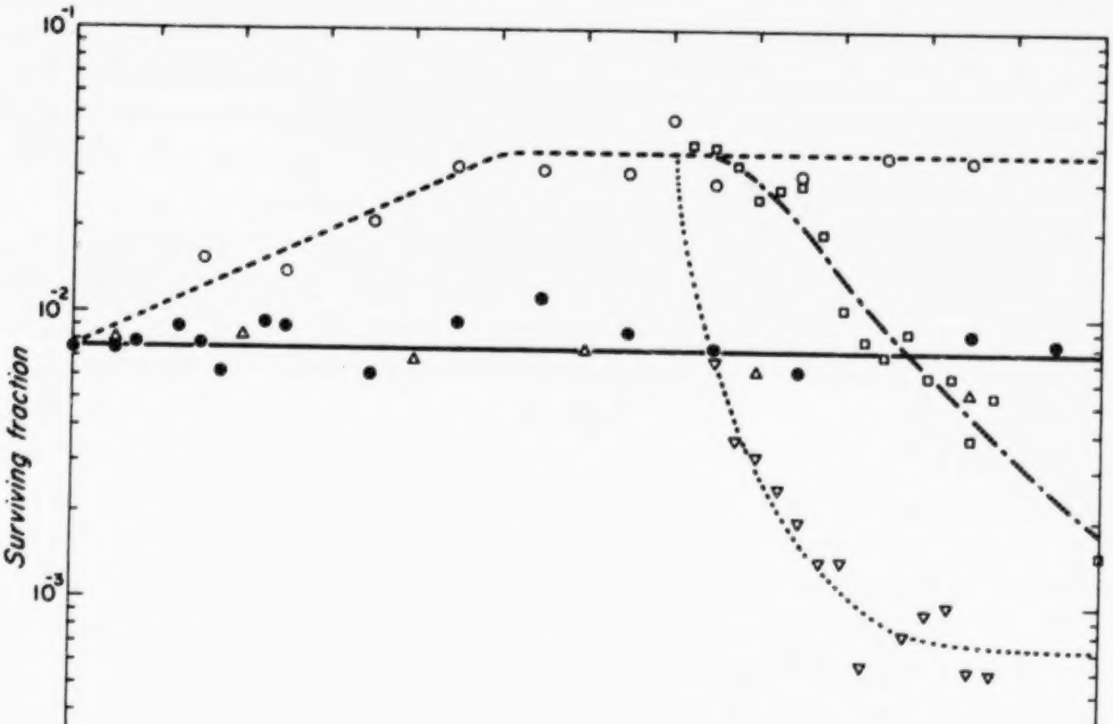

Figure 12. Survival curves for mouse L-cells exposed to 1,000 rads at the times shown for the populations described in figure 11: ●, control; ○, methotrexate alone; □, methotrexate plus Leucovorin; and Δ given methotrexate plus deoxyadenosine.

ments measure the same type of damage? Do the experiments under conditions of reduced metabolism reduce the number of repairable lesions, or do they foster the repair process at the expense of processes that bring about lethality? Are we dealing with only one type of lesion when we consider radiation death or are there a variety of lesion types? I must say that we do not have a definite answer to any of these questions, but my feelings would be the following: The single-dose and two-dose fractionation experiments are concerned with the same type of lesion because, in general, if we apply conditions that give maximum protection prior to the first dose in a split-dose experiment, then we see little or no effect from the split-dose. It is also my feeling that the lesions that are not expressed under conditions of reduced metabolism are the same lesions that are repaired in either the split-dose or the post-treatment experiments. As to whether we are dealing with one lesion or many types of lesions the evidence is less clear, but my present feeling is that there are at least two types of lesions—repairable lesions of the type we have been discussing and lesions not repairable (at least under any of the conditions we have found today). It is obvious that much remains to be done.

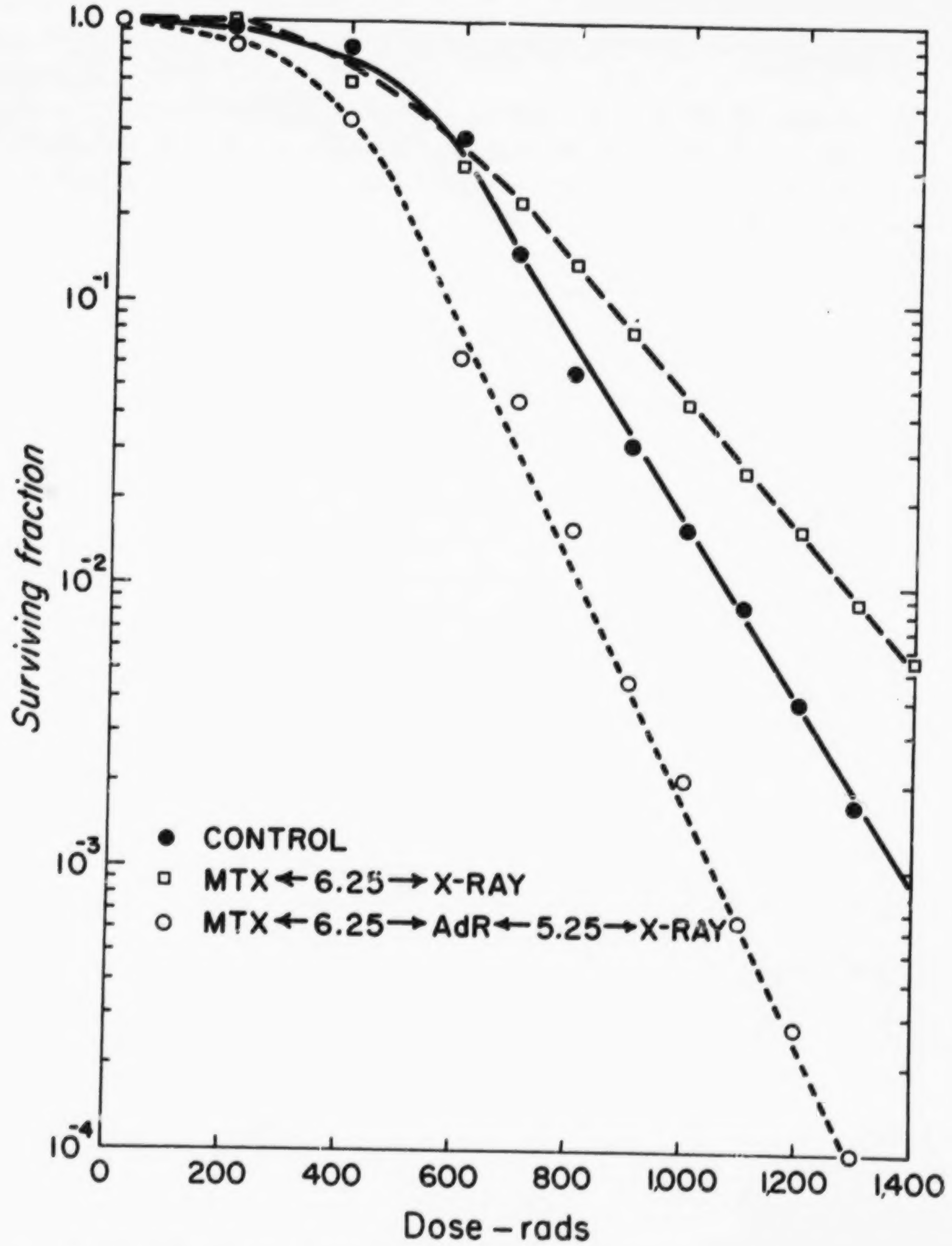

Figure 13. Survival curves for mouse L-cells: ●, control population; □, population treated with MTX for 6¼ hours prior to irradiation; and ○, population treated with methotrexate for 6¼ hours followed by deoxyadenosine for 5 hours.

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CYTOGENETIC EFFECTS OF IRRADIATION

John D. Abbatt

Cytogenetic changes in the shape of chromosome and chromatid aberrations have been observed in many tissues both plant and animal following the work of Sax (*1*) and others in the 1930's and 1940's. Work in man in the 1940's and 1950's has been accelerated by improvements in technique and particularly by the development of tissue culture methods that permit observation of the chromosomes of dividing cells (cells in mitosis).

It must be emphasized that ionizing radiation is only one of many agents—chemical, physical, and viral—known to produce changes in chromosomes. Though radiation is a potent agent, it must be regarded as only one agent producing a change in the nucleus and not as a specific agent producing a specific change; therefore, these changes and their consequences are not peculiar to radiation alone.

The nature of the changes induced in chromosomes is now well known in descriptive terms as seen through conventional microscopes operating at their limits of resolution. Chromosome-type aberrations will be discussed later and consist primarily of the following types:

1. Centric rings.
2. Acentric rings.
3. Symmetrical interchanges of translocations.
4. Complex polycentrics.
5. Inversions.
6. Interstitial or dot deletions.
7. Terminal deletions.

Those normally scored by cytologists are 1, 2, 4, 6, and 7 only.

Chromosome-type aberrations are scored particularly in radiation studies on peripheral blood cells. These cells are normally mitotically inactive and remain in the pre-DNA synthesis (G1) stage of interphase; that is, all the cells are in the same state of development and are therefore more likely to show a consistent and uniform response to radiation. Even more important, only chromosome-type changes are seen in cells irradiated in the G1 state; chromatid changes and subchromatid changes are induced in cells irradiated in later stages of interphase or mitosis. In other words, by studying chromosome changes in any radiation work, one is concentrating on the simpler and more scorable part of a very complex series of changes that occur.

Chromatid-type aberrations are of course aberrations in which the unit damaged is the single chromatid and are characteristic of a cell affected during the DNA synthesis (S) and post-DNA synthesis (G2) stages of interphase. These aberrations in chromatids can arise spontaneously and are in general "easier" to induce both "in vivo" and "in vitro" than are chromosome aberrations.

Lymphocytes of the peripheral blood are commonly used for study in man. The reasons for choosing this material are the ready accessibility of blood and because the lymphocytes do not normally divide in the peripheral blood. This latter reason is thought to be an advantage in that the population of cells sampled is considered to be uniform and in the G1 state.

This assumption of uniform state and of a subsequent uniform response to radiation and other stimulae would be, if true, of considerable value. The lymphocytes are not morphologically distinguishable from one another, but it is now virtually certain (*2*) that there are two or more distinct lymphocyte populations whose lives vary from a few days to many months, and it would not be at all surprising to find that from a functional and response point of view a "newly hatched" lymphocyte, from say the thymus, was very different from a 9-month-old lymphocyte whose origin was in the spleen or the mediastinal hilar nodes. In man, this is a speculative area, but in certain animal studies differences in response appear to exist. An improved understanding of the kinetics and function of peripheral lymphocytes is essential before the question of the best sampling tissue can be resolved.

Studies of cytogenetic changes based on a technique so far removed from a mechanism or mode of action within the genetic material are necessarily indirect. Such studies are undertaken since our present state of knowledge is incomplete and does not allow more sophisticated and direct observations to be made. It is important, therefore, that we should not delude ourselves that we are observing more through a conventional microscope than is really the case. What is seen is one static piece of presentation on the nuclear stage and not a complete production; it is certainly not a dynamic view of the conductor itself in action.

Comment on Present Cytogenetic Radiation Studies

It has been established that radiation can and does produce cytogenetic changes in both plants and animals. In plant and certain animal systems, the chromosome changes induced have been correlated "in vivo" and "in vitro" with absorbed external radiation dose and the correlation seems to be very good even at low doses of a few rads (*3*). The situation is almost certainly the same in man, and "in vitro" studies, for example, on irradiated blood have almost uniformly demonstrated an aberration against physical dose correlation which is just as good as that shown in plants.

Human "in vivo" studies are not so advanced, and different laboratories have reported results that, while being in general agreement, are not entirely consistent with one another. In part, this is due to differing techniques, to the study of different aberrations and to the relatively small number of studies so far undertaken; however, a major part is undoubtedly due to a lack of aberrations to be observed arising from the low yield of aberrations and the large number of ceils that must be screened and scored, even in each individual.

The laboratory technique of cytogenetic study will not be discussed, but it will be remembered that a blood culture technique is involved, followed by microscopy and complex microscopic human scoring. Human interpretation differs with different observers and fatigue and boredom are important limitations. The technique is very time-consuming and laborious. This, the technique, being relatively complex and tedious, has itself so far limited its large-scale population application in man, particularly, as will be seen later, where aberration yields are normally low.

This problem of population scanning will not foreseeably be overcome without the application of computerized scanning and analytical methods of analysis. These techniques are now being developed but are not yet in use.

The studies reported in man are of two main types.

1. Clinical Studies:

The literature now abounds in cytogenetic clinical studies. Studies of individuals are often performed as clinical "tests" and frequently as a diagnostic measure to confirm, for example, a diagnosis of mongolism. The majority of the syndromes, which have been identified and described and which are associated with identifiable cytogenetic and physical abnormalities, are associated with the XY or sex chromosomes. A recent example of this clinical-type study that is being extended on a "population" basis, albeit a small one, is a British study already the subject of a preliminary report by Court-Brown et al. from Edinburgh (*4, 5*). This study has shown that in a number of subgroups of the British criminal population there is a cytogenetic disorder associated with the aberrations of the XY chromosomes, and that this is associated with increased stature, with crimes of violence and an aggressive personality. These personality deviations or traits and the cytogenetic abnormality are apparent from birth or early childhood and are reflected in the incarceration of the individuals concerned in institutions in childhood, and later in prisons. The antisocial behavior and almost continuous incarceration of these individuals is so marked that it has not been possible to determine their fertility, since virtually their whole lives are spent segregated from the opposite sex.

2. Population Studies:

Few true population studies have been reported, though possibly the studies on criminals mentioned above should be included in this group. The only true population studies, however, that have been carried out, particularly in the context of irradiation, cover a large number of small groups of people. These groups may be divided as follows:

a. Individuals exposed to high levels of natural background radiation. Chromosome aberrations have been claimed to be present in some of these individuals (Brazil). The quality of the cytogenetic work from these studies makes this claim difficult to assess though such a finding would not be unexpected. Some evidence exists to suggest that cytogenetic study in the tropics may require modification of "temperate" or "air-conditioned" techniques, and this may well be a reason for the technical difficulties that have arisen in this connection.

b. Workers exposed to occupational radiation exposure—levels at and below ICRP recommended occupational exposure levels. These studies carried out particularly in the United Kingdom (*6*) and France clearly suggest from present reports that slight but definite increases in chromosome aberration incidences exist in populations exposed to low levels of chronic occupational radiation.

c. *Persons exposed to diagnostic medical radiation.* Studies in this area show unequivocally that low yield but definite chromosome aberrations follow these procedures. (These data are in particular need of calibration.)

d. *Persons exposed to medical radiotherapeutic procedures.* Chromosome aberrations occur constantly after radiotherapeutic exposure. Though calibration is still lacking, the yield is higher than that following diagnostic procedures and therefore appears to be related to dose.

e. *Human accidental exposure.* Human accidental exposure gives similar finding to the post-therapeutic picture, and, in fact, cytogenetic studies have in a number of instances provided evidence of appreciable exposure or lack of such exposure where physical dosimetry was absent or misleading.

f. *Personnel exposure to fallout and nuclear explosions.* Personnel exposed to fallout and nuclear explosions have been studied to a limited extent and not all currently studied populations have yet been reported; however, it is apparent from Japanese reports that the expected yield of chromosome aberrations do, in fact, occur following exposure to mixed fission products and neutrons. In this context, the results of U.S. studies currently being undertaken on the Marshallese are of particular interest (*10*).

In all these population studies relating to radiation, though there is uniform evidence of a correlation between aberration incidence and dose received, the amount of data is still quite inadequate to provide a firmly calibrated system relating biological damage and dose. The work of Bender et al. (*7*) and to a lesser extent that from other groups, such as Norman Jacobs et al. (*8*), Fischer et al. (*9*), and our own Ottawa laboratory, suggest that this calibration can be achieved, and, much less certainly, that a differentiation between whole- and partial-body radiation and neutron and x irradiation will be possible.

Calibration for Radiation Exposure

There are two firmly proposed methods of calibration and both must be used:

1. "In vivo" cell irradiation in the body with subsequent culture and aberration assessment. Irradiation dose known; that is, DIRECT.
2. "In vitro" cell culture and irradiation outside the body with subsequent aberration assessment; that is, INDIRECT.

Calibration is, of course, essentail before cytogenetic changes can be used as an indicator of damage relating to dose. (It is at present fashionable to refer to "biological dosimetry," but this may be a misleading term at least for cytogenetic work, and "biological indicator of damage" is preferable.)

Both methods of calibration of this type of system and any extension of cytogenetic population studies beyond very small populations require a radical change in cytogenetic study techniques, since the amount of work involved is enormous. Recently, much work has been devoted to the development of automated chromosome assay techniques; it is only by the development of such a technique or techniques to the point where they are applicable and usable on a large scale that cytogenetic studies can be extended to true population studies.

Such an extension—including its calibration—will of course produce a large number of extremely useful "byproduct." One of the most obvious will be the ability to relate biological damage to physical radiation dose in individuals; however, the evaluation for prognostic purposes of the significance of this damage (exposure) may well have to await the outcome of long-term cytogenetic studies designed to elucidate mechanisms of radiation action.

Interpretation of Cytogenetic Changes

Present interpretation of the significance of cytogenetic changes is much hampered by a lack of knowledge of the mechanism and mode of action involved in:

1. Inducing the observed changes (of which in any given case probably only a portion are scored even by good cytology).
2. The detailed mechanism of chromosome and nuclear control of the cells.

An example, which illustrates the extent of this lack of knowledge, is that though we know that radiation and a number of other chemical and viral agents can, in certain circumstances, be mutagenic; we are not able to define the circumstances under which this mutagenesis occurs; we can only speculate on the mechanism of mutagenesis.

It is presumed with some reason that the structural changes associated with chromosome damage are connected with the mutagenic agents inducing these changes. The two phenomena, that is, structural changes and mutagenesis, are not necessarily and certainly not always cause and effect.

It is now realized that neoplasia is in the majority, if not in all cases, a multicasual affair, and this represents a major change in our views in the last 10 to 15 years. In this context, it is useful to speculate briefly on the subject of aberration yield—a high-population yield of aberrations would be 1 percent, and it is much more likely to be 0.5 percent. Though this sounds small, it represents a very large number of changed cells when one remembers that there is every reason to believe that this represents the percentage of changed cells throughout the exposed individual's body. Though certainly not all of the 0.5 to 1 percent are capable of reproduction; that is, division, many are and we already know that there is a low incidence of gross changes discernible in such a changed irradiated population of animals or man; ergo the changes leading to (for example) neoplasia are not necessarily, and certainly not entirely, the ones seen as aberrations. It may well be that the changes we see include a small and as yet undistinguishable proportion of "significant" changes though this is entirely speculative.

Cytogenetic study with present techniques is a rather gross morphological method conducted well above the macro-macromolecular level and if this technique is to be fully exploited at this level a large amount of information is necessary, relating both to large numbers of people and to all of the chromosomes. Only from this type of data will it be possible to derive information in detail relating to less gross changes in chromosomes other than those of the sex chromosomes.

It is probable that the sensitivity of the system will be good for exposures of a few rads; that is, down to 5 to 10 rads or less. Certainly, the "in vitro" work on human blood and the limited amount of work on occupationally exposed populations suggest that this order of sensitivity will be readily obtainable. The part played by whole- and partial-body radiation has not yet been fully evaluated, but the work of Bender and Gooch (7), though not yet confirmed, suggests that a differentiation between neutron and other types of radiation will be possible. It appears that observations must be made soon after exposure in these circumstances if a differentiation between whole- and partial-body irradiation is to be possible.

Only when it is possible to apply the cytogenetic technique to adequately executed human epidemiological studies will there be any real chance to derive somatic genetic information.

The magnitude of this type of operation must not be underestimated, since not only will it involve the application of automated cytogenetic techniques and automated blood culture, but also high-grade epidemiological ecological studies on man. (Since man is the subject and object of study as well as the investigator, there is little doubt that the human, that is, epidemiological end of this operation, will prove to be the most tedious, frustrating, and expensive part of the investigation.)

Having commented on the difficulties, we should now look briefly at some of the information that may be derived from this type of work assuming that it has been done. A large-scale population study will provide a "chromosome map" of the population studied, and if this map is related to information derived from record linkage studies, "Pandora's box" will provide objective information on such widely varying and important subjects as:

1. Marriage guidance and eugenic advice;
2. Pesticides and their human effects;
3. The effects of food and drink and their additives;
4. The side effects of drugs;
5. Industrial chemical and environmental chemical contamination;
6. Radiation dose or exposure, and lastly, and probably most important;
7. Information relating to the method of action of the genetic material of the cell both in health and after damage.

Before this somewhat utopian type of information can be obtained, we must first learn how to apply the techniques involved in relatively simple situations. A large number of examples are possible, but for the sake of brevity only one will be given.

The study of hard-rock miners will yield valuable information. It is known that the radon levels in hard rock metal mines overlap the radon and the radon daughter levels in uranium mines. It is known that this latter order of airborne hazard is causatively associated with lung cancer and possibly with other lung diseases, and it is reasonable to expect with some confidence that similar and probably smaller changes occur in hard-rock metal miners.

Hard-rock metal miners constitute a very large population in a number of countries, particularly when compared with the uranium mining population. If they are to be adequately investigated, the following factors should be determined:

1. The exposed population must be defined as a suitable and equal or preferably larger control population(s).
2. The defined exposed and control populations must be completely followed to extinction (that is, death).
3. All factors known or suspected to be involved in a mechanistic manner in any changes should be studied, both in the exposure environment of individuals and in their bodies. This investigation must be carried out on a continuous basis and in a serial manner. Factors such as smoking, exposure to dust, and other chemical carcinogens or cocarcinogens must be quantitatively evaluated. Metabolic balance studies will probably be necessary on subpopulations; that is, sample populations studied. These subpopulations, if properly and randomly selected, can be quite small.
4. Cytogenetic study should be carried out serially on the whole population.

It would seem reasonable, and in fact necessary, to marry the technique of cytogenetic analysis with other epidemiological data-collecting operations and this proposed population. If the survey includes adequate health control measures as it should, the problems of obtaining small and relatively infrequent samples of blood will be minimal. The reward will be vast and will include information not only on radiation but on the effect of aging and cell ploidy, and so forth.

Other populations suitable for study immediately come to mind; certainly, all the groups listed earlier as having been studied in a fragmentary way should be adequately extended. Particular attention should be paid to newborn children and the products of conception, particularly following maternal irradiation in the first trimester of pregnancy.

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METABOLISM OF RADIONUCLIDES IN WORKERS

Gordon C. Butler

I propose to give you some general and personal observations on this subject. These have occurred to me during the past 3 years as a result of my work in an ICRP Task Group on "Evaluation of Radiation Doses to Body Tissues from Internal Contamination due to Occupational Exposure." Everything I say will be slanted toward this practical objective. I may tend to oversimplification for emphasis and in order to stimulate discussion. In producing concrete examples, I will use only the 30-odd radionuclides considered in the Task Group Report now in the press.

The metabolic behaviors of radionuclides may be divided into three classes: simple, complex, and awkward. The differences are most readily seen in the mathematical equations describing their retention and excretion. The fractional retention of a radionuclide with a simple metabolism is described by an equation with one or two exponential terms: examples are tritium oxide, sodium chloride, iodine, polonium 210, and so forth.

SIMPLE

$$R(t) = ae^{-\lambda_1 t} + be^{-\lambda_2 t}$$

COMPLEX

$$R(t) = ae^{-\lambda_a t} + be^{-\lambda_b t} + \ . \ . \ . \ + je^{-\lambda_j t}$$

or

$$R(t) = At^{-n} \qquad (0 < n < 1)$$

$$Y(t) = nAt^{-(n+1)}$$

AWKWARD

$$R(t) = 1$$

$$Y(t) = nAt^{-(n+1)} \qquad (-1 < n < 0)$$

Radionuclides with "complex" metabolisms generally are bone-seekers. Their fractional retention is described by equations with several exponential terms (5 for radium, 4 for strontium), so many as to be unwieldy. A simpler formulation can be made by a power function which usually fits the data from a few days to a few decades. This may need modification to fit early times. If the early observed points lie above a straight line on a log-log plot, an exponential term has been used to describe these. If the early observed points lie below the straight line, modified equation of the form $R(t)=A(t+x)^{-b}$ can be used. Some log-log plots of experimental data show late observations falling below the line; that is, the curve "tails off." These can be brought into line by using an equation of the form $R(t)=At^{-b}e^{-\lambda t}$ where λ is small. At large values of t, the exponential factor takes over. As a result of my experience with this ICRP exercise, I believe that far too much time is spent in fitting curves to retention or excretion data and devising equations to describe the change of these variables with time. I believe, with Scorer, that "what is required is that no more data or more powerful principle than is absolutely necessary should be used" (*1*). For dose assessment what is required is an omnibus equation that can be fitted roughly to the retention of any radionuclide and used for computer calculations of the area under the curve.

The best examples of radionuclides with an "awkward" metabolism are thorium and plutonium. Thorium is not excreted enough to reduce the body content significantly nor to permit the calculation of body content from excretion rate. The awkwardness with plutonium is that one can't explain retention and excretion with a single system of equations; for example, excretion equations, which fit most experimental data, have an exponent the absolute value of which is less than 1. This means that on integration one obtains a retention equation with a positive exponent, which is absurd. Another mathematical difficulty is that if one integrates the excretion function over an infinite period to obtain an estimate of the body content the answer amounts to less than 10 percent of what it should.

By this time some of you will be wondering why I am talking so much about these equations. There are several reasons for this. One is that a retention equation is central to the calculation of body content and radiation exposure. Differentiation of the retention equation gives the fraction of body content excreted per unit time as a function of time after contamination. Integrating the retention equation and multiplying the integral by the μCi initially present gives the radiation exposure in μCi-days from a single intake. Another reason for needing these equations is to calculate the accumulation of a radionuclide with chronic or multiple exposures. I will have more to say about this later. Finally, we had more trouble in getting agreement of the Task Group to the presentation of the mathematics than with any other part of the report.

Much use has been made of compartmental models to illustrate the metabolism of radionuclides and to help in the mathematical formulations. The so-called catenary system (fig. 1) has been known for many years in the sequential buildup and decay of the members of a radioactive series (*2*). These were described by Bateman in 1910 by a series of linear differential equations (*3*). In the mammilary system the same kind of equations result and the retention in the central compartment can be described by an equation with one exponential term for each compartment. More complicated models with *n* peripheral compartments have been proposed by Bernard (fig. 2), and by Marshall (fig. 3), to describe the retention of bone-seekers with "complex" metabolism (*4–6*). These compartmental models have made interesting intellectual exercises but they haven't made a great practical contribution to the assessment of radiation doses; in fact, there is one serious objection to this approach in that it tends to direct attention principly to the location of the radionuclide rather than to its chemical form.

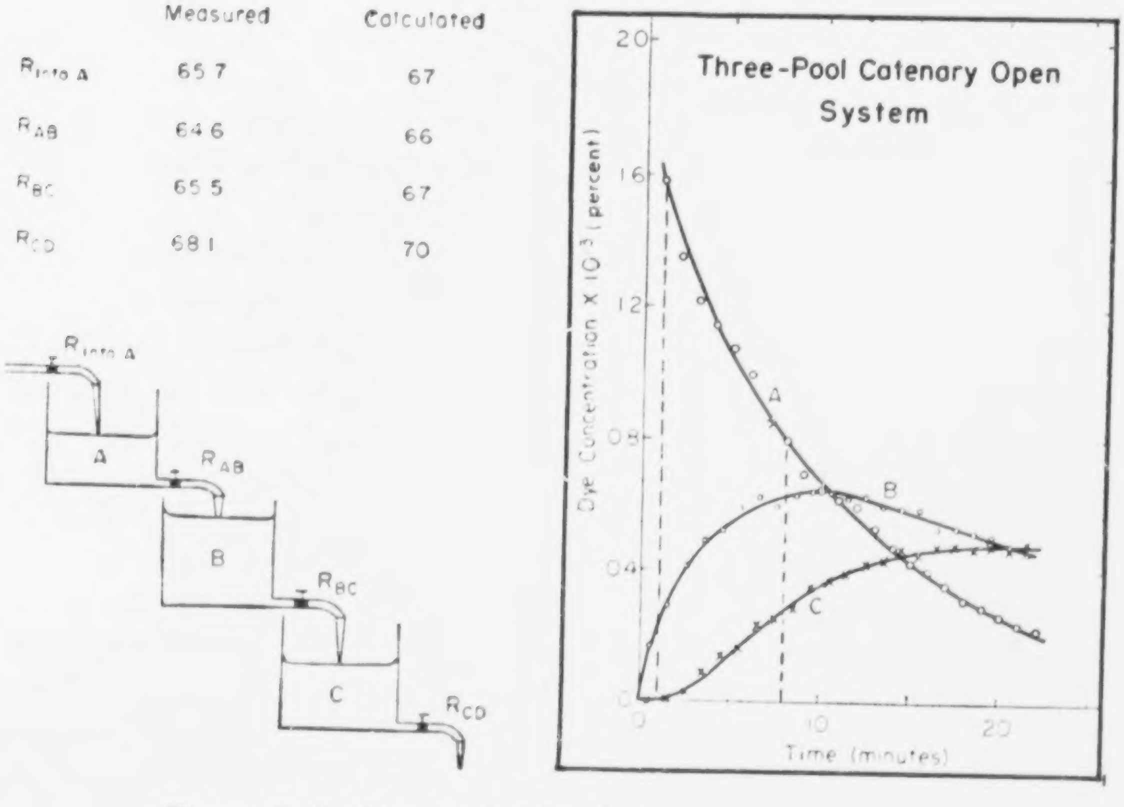

Measured
Calculated
$R_{into\ A}$ 65.7 67
R_{AB} 64.6 66
R_{BC} 65.5 67
R_{CD} 68.1 70
$R_{into\ A}$
A
R_{AB}
B
R_{BC}
C
R_{CD}
Three-Pool Catenary Open System
Dye Concentration × 10^{3} (percent)
2.0
1.6
1.2
0.8
0.4
0
A
B
C
0
10
20
Time (minutes)

Figure 1. Radium series buildup and decay system.

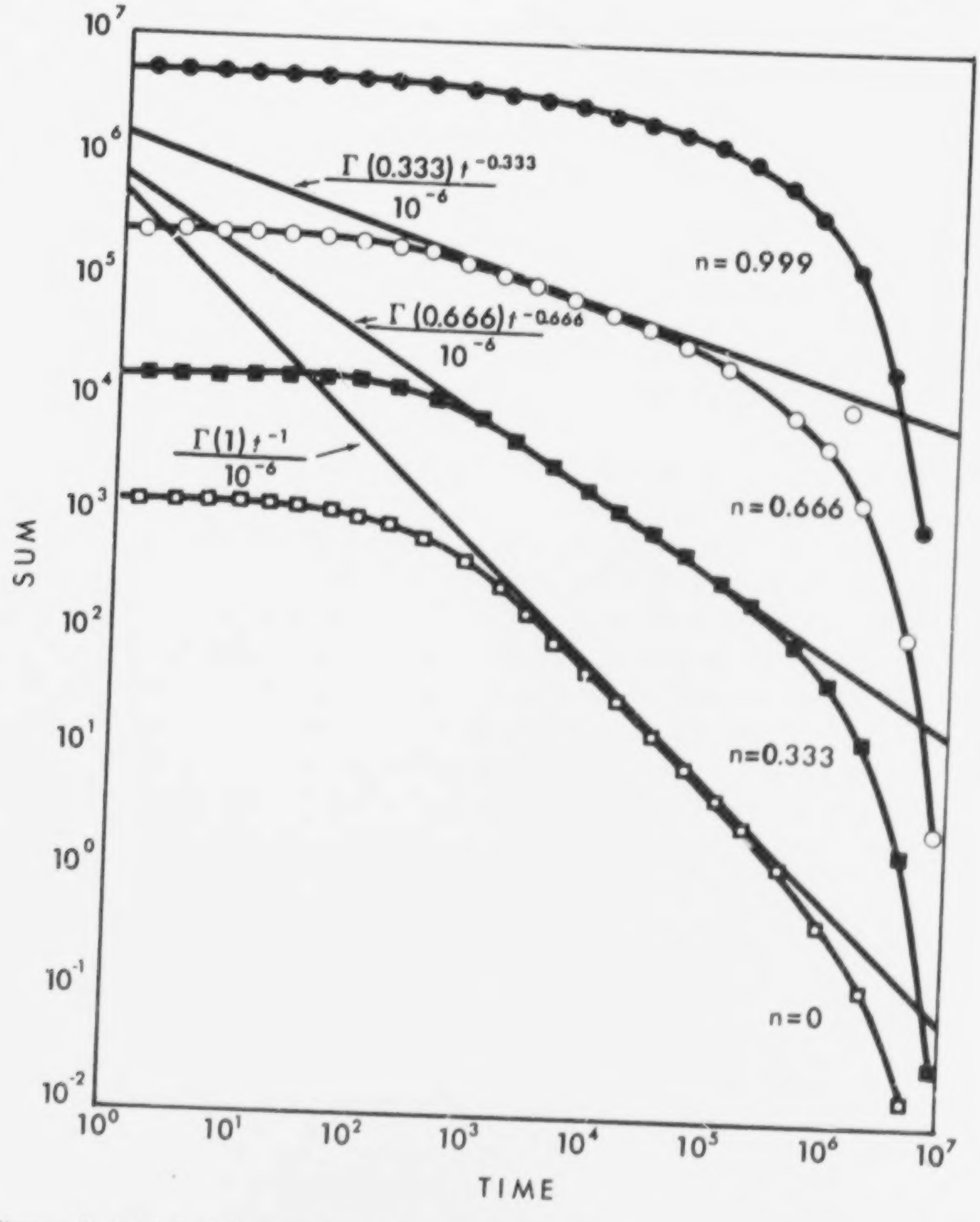
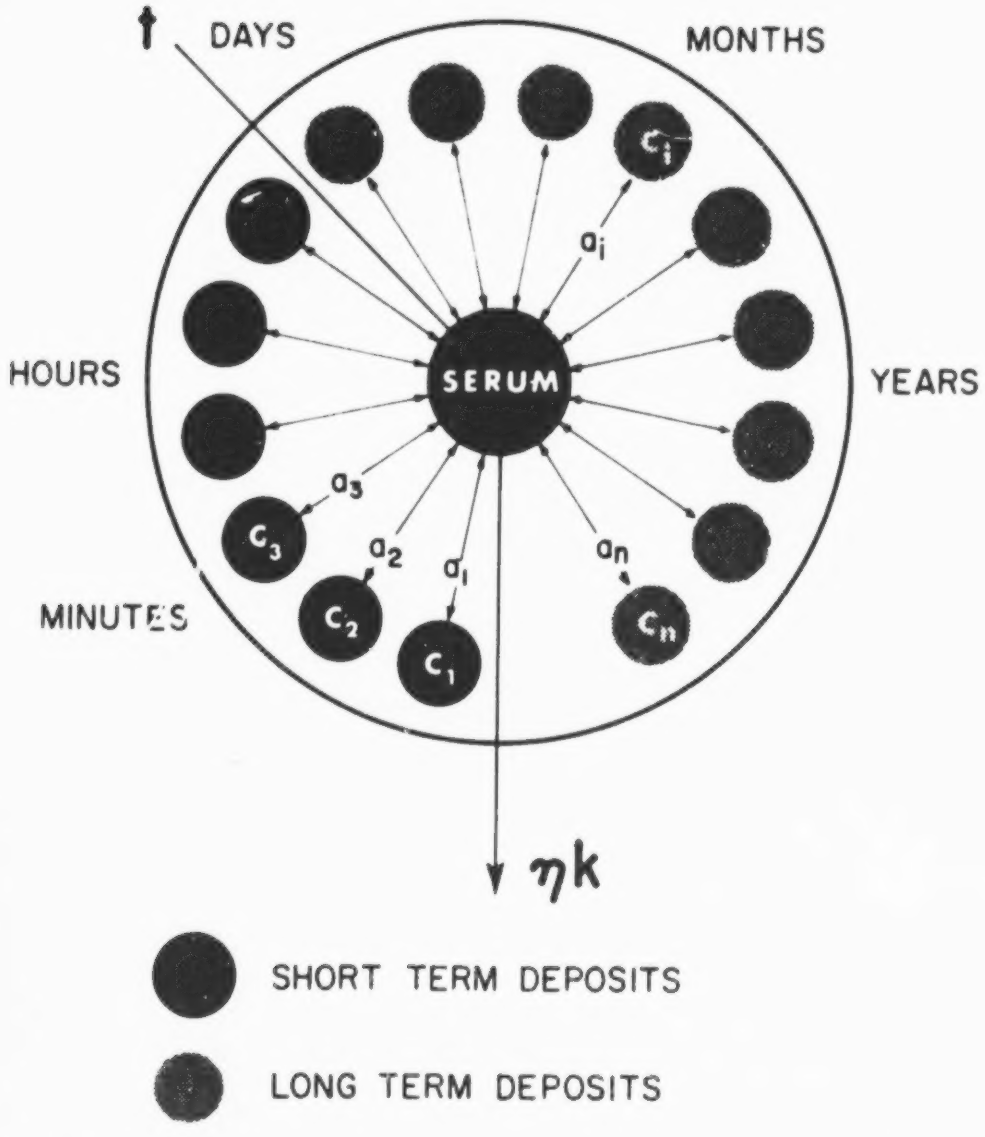


Figure 2. Model with *n* peripheral compartments for calculating the retention of bone-seekers.

The fundamental importance of the chemical form of an internal contaminant is often overlooked. Obvious examples that come quickly to mind are tritium and carbon 14. Almost as obvious are iron 59 (inorganic and hemoglobin) and cobalt 60 (inorganic and vitamin B_{12}). There are a number of others that are less obvious. Following the entry of an inorganic selenium compound into the body as much as one-third of it may be rapidly excreted as dimethyl selenide in exhaled


t
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c_1
a_n
c_n
ηk
SHORT TERM DEPOSITS
LONG TERM DEPOSITS

Figure 3. Retention of bone-seekers with "complex" metabolism.

air and the rest more slowly as some inorganic compound in urine: thus a biphasic retention curve for selenium is really for two different chemical compounds. Dr. Hollins in our laboratory has also demonstrated a biphasic retention curve for tellurium, although the excretory product in the first phase has not been proved to be dimethyl telluride. He and others elsewhere have indications that there may be a considerable difference in the metabolism of sodium tellurite and sodium tellurate in rats. Thomas and Stannard showed that polonium injected intravenously in 0.5N HCl or 0.15 M sodium citrate disappears slowly from the blood of rats whereas in a neutral solution of 0.9 percent NaCl removal is much more rapid. A final example is the graph (fig. 4) familiar to most of you, displaying the difference between the urinary excretion of tetravalent and hexavalent uranium in man (7). These differences in metabolism with chemical form have a number of practical implications:

1. The radiation dose may be quite different with different chemical forms.

2. The identification of the chemical form of a contaminant might provide important information about the contamination event.

3. There is very little knowledge of the chemical form in which internal contaminants are excreted. In this area we might gain more insight into the details of metabolism and excretion that would help in attempts at therapeutic removal from the body.

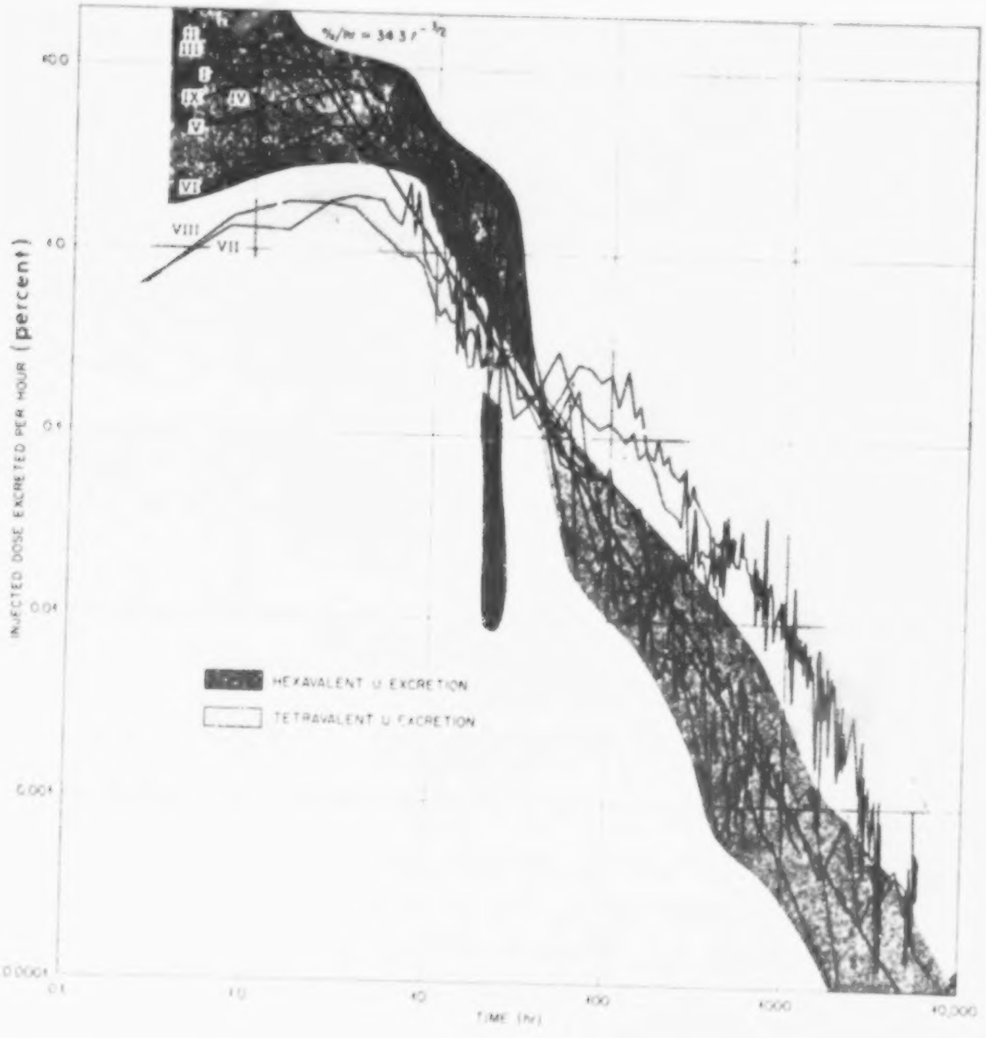

Figure 4. Urinary excretion of tetravalent and hexavalent uranium in man.

The work of the Task Group has made us aware of another extension of our studies, in addition to this chemical problem, required in assessing doses from internal contamination. ICRP Committee 2, in its Publication 2, used as the model a constant intake on every working day resulting in a constant content in the critical organ and limited by a maximum permissible dose rate. The Committee 4 Task Group used as its model a single intake of short duration resulting in a varying content in the critical organ and limited by a maximum permissible dose. It is now obvious that this simple approach needs to be extended to recurrent intakes over some longer period, limited also by a total dose or dose commitment. The situation to be considered is illustrated by the diagram (fig. 5);

where,

q_{ch}= the accumulated body content after chronic exposure for time T, and

t= the time at which the accumulated dose is estimated.

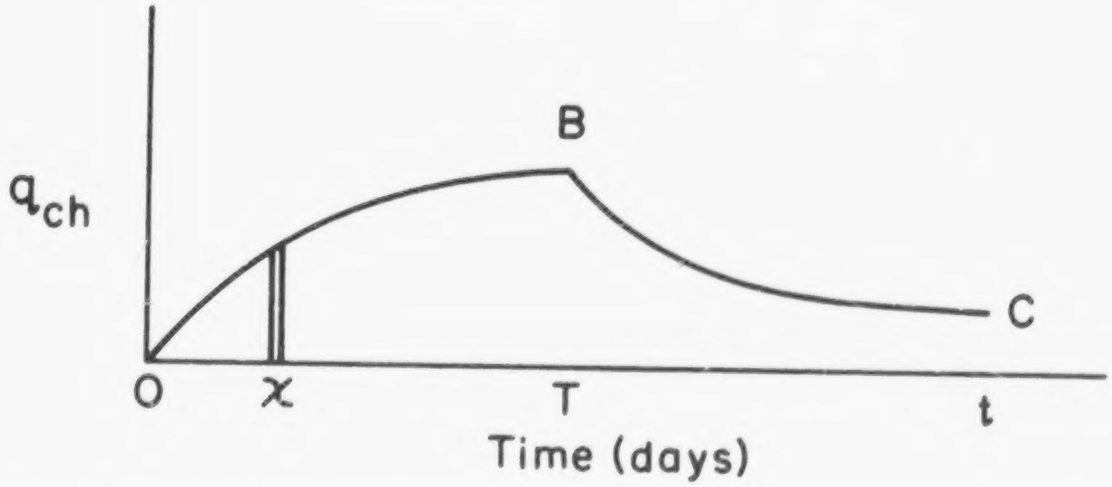

Figure 5. Accumulated body content (q_{ch}) after chronic exposure for time (T).

A system of equations for describing retention *OB* and *BC* was developed to assist in calculating the areas under these curves and the radiation exposures resulting from chronic uptake. Similar exercises have been reported by Müller et al. (*8*), Shamov (*9*), and Robley Evans (*10*). Some unification and simplification were possible with the help of A. Veld and F. Breuer.

One general equation for calculating the area under this curve is not available. Under certain conditions simplifications are possible:

When t is very long with respect to T.

For a total intake of A microcuries uniformly distributed over T days,

$$\text{area } OBC = A \int_0^{18000} R_s(t)\, dt$$

For an initial rate of intake A/T declining with time according to some $f(x)$,

$$\text{area } OBC = A \int_{x=0}^{x=T} \int_{t=0}^{t=18000} f(x)\, R_s(t)\, dx{\cdot}dt$$

When t is comparable with T,

For a total intake of A microcuries distributed uniformly over T days,

$$\text{area } OBC = A/T \int_0^T \left[\int_0^{t-\xi} r_s(\eta)\, d\eta \right] d\xi$$

When the rate of intake is declining with time according to some $f(t)$ such a simple formulation is not possible and the total area must be represented by the sum of the area under OB plus the area under BC.

One frequently encounters the proposition, "Are radionuclides received chronically metabolized differently from those received in a single short intake?" The decline with time of the body or organ content of a radionuclide with a "simple" metabolism is practically independent of the time over which the content was accumulated. This is illustrated in figure 6 showing the retention of cesium 137.

The situation is quite different with radionuclides exhibiting a "complex" metabolism. As the period of accretion T becomes longer the subsequent decline becomes slower. Once presented, this conclusion seems obviously logical. As T, the period of intake, increases, higher and higher proportions of the body content reside in "deeper and deeper compartments." This is shown in figure 7 where the body contents of strontium 90 resulting from three different patterns of intake are plotted.

Other examples of these differences are:

Morrow, Gibb, and Leach reported that UO_2 inhaled by dogs was eliminated more slowly after chronic intake than after a single intake (table 1).

These half-times are to be compared with 120 and 180 days for a single intake *(11)*.

Lippman et al. found a different distinction between the two types of exposure (fig. 8) *(12)*.

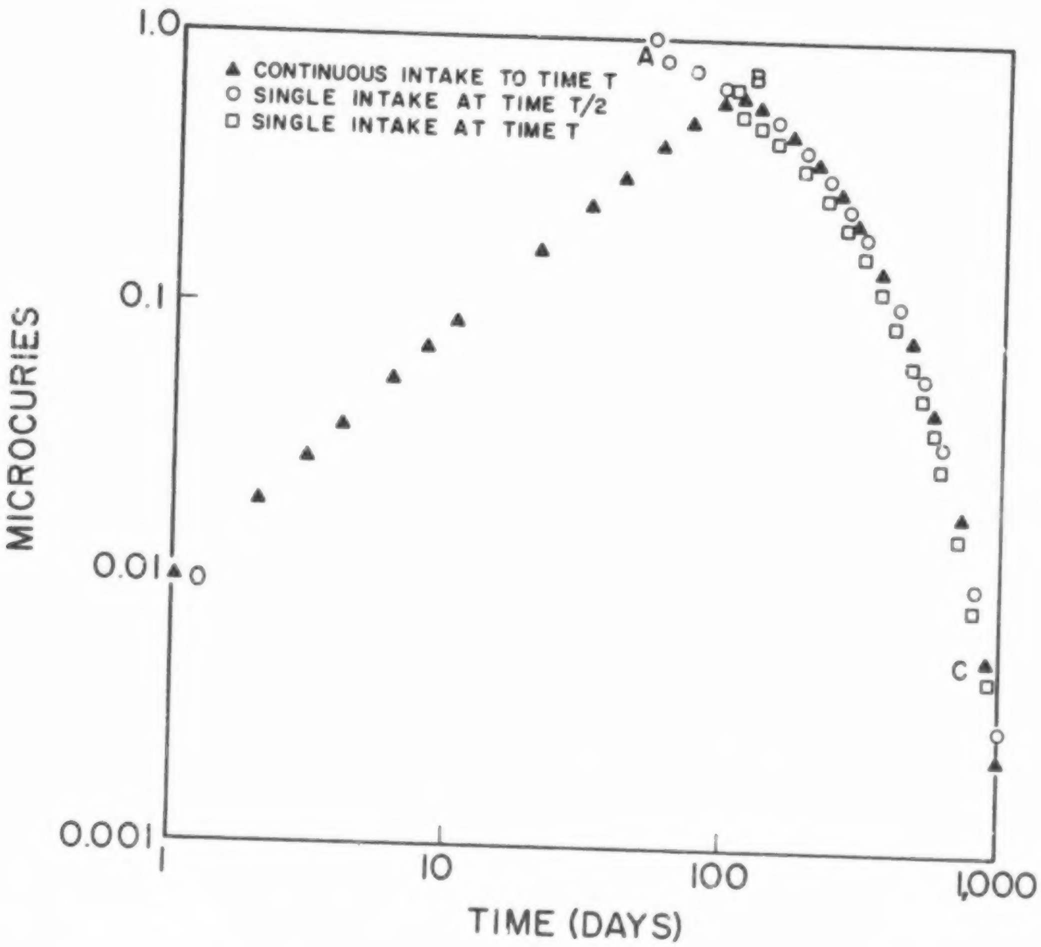

Figure 6. Cesium 137 retention.

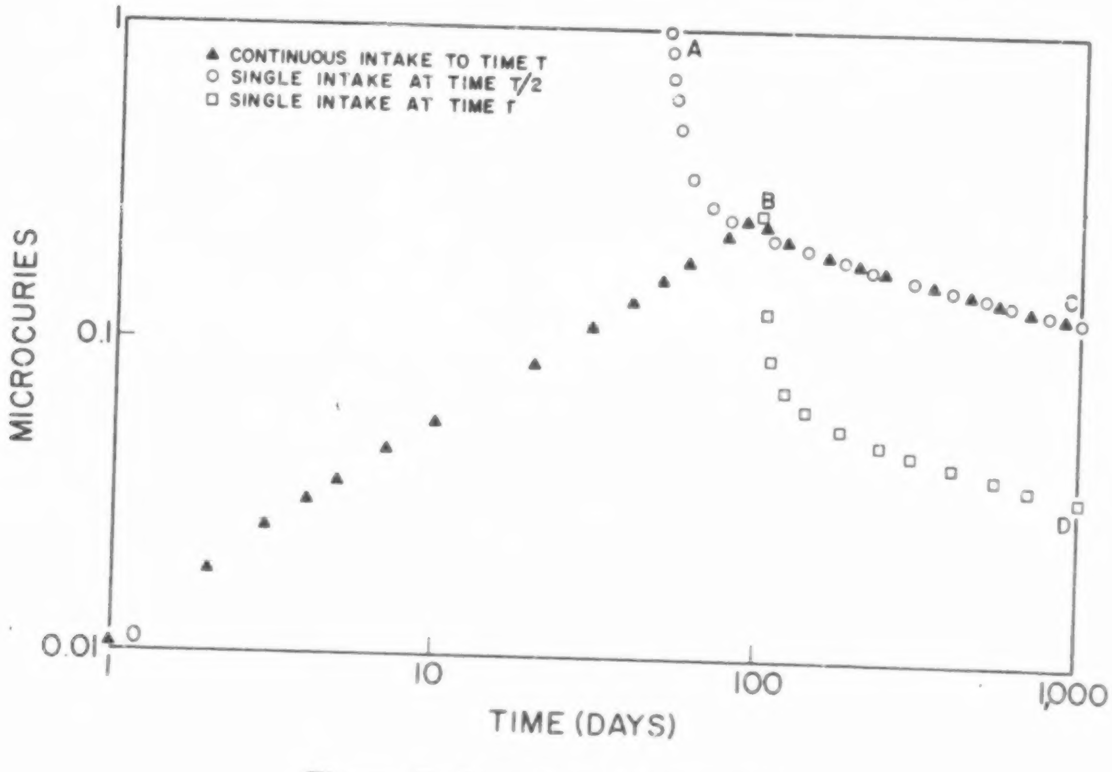

Figure 7. Strontium 90 retention.

Table 1. ***Lung retention of UO_2 following multiple inhalation exposures***

Species	Duration of exposure (years)	Post-exposure time [a] (days)	Biological T/2 (phase II)[b] (days)
Rats	1	380	280
Dogs	5	800	400
Monkeys	5	350	320

[a] Time after cessation of exposure over which clearance measurements were made.

[b] Clearance slope based on 2 to 4 animals of each species sacrificed at each of 3 or more points in time.

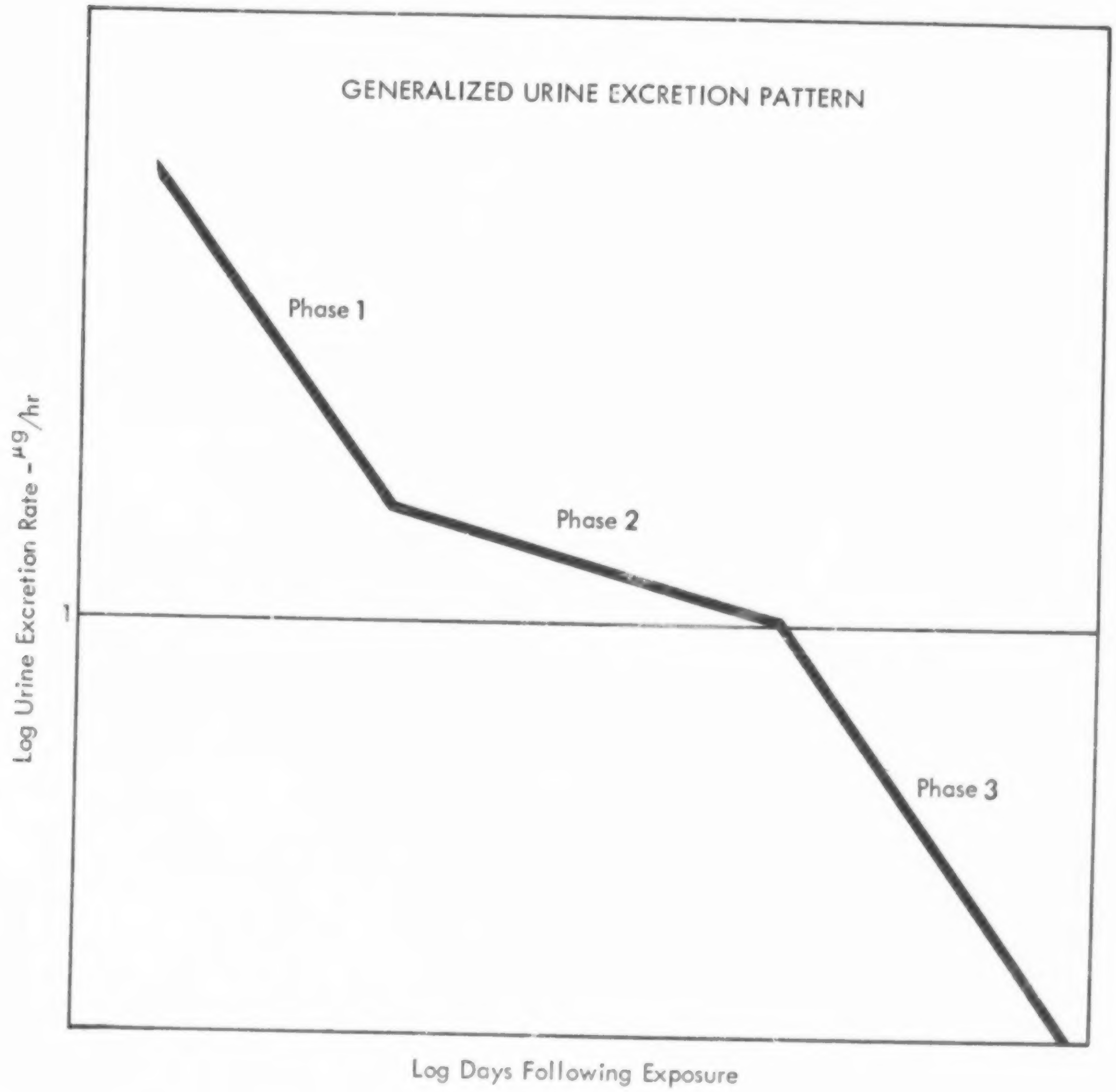

Figure 8. Generalized urine excretion pattern to serve as a model for the estimation of future excretion and body burden on the basis of current data.

There is evidence that multiple uptakes of plutonium give an internal distribution different from that resulting from a single intake. After a single intravenous injection the highest concentration of plutonium is found in the bones. In workmen chronically exposed the concentration in lungs is higher than in vertebrae but this may be due to the difference between the chemical forms of plutonium in the two cases. Another difference in distribution is between lungs and lymph nodes. It is obvious that soon after inhalation there will be more plutonium in lungs than in pulmonary lymph nodes and this situation persists after single inhalations in dogs. On the other hand, in seven of the nine chronically exposed workers, described by Langham et al., the concentrations in respiratory lymph nodes averaged seven times those in lungs (*13*). This should be of considerable practical interest in the practice of radiation protection.

Thus far, I have said nothing about Guidelines to Radiological Health, although the Task Group made two contributions to this subject. The total doses of radiation received (or committed during the worker's life) resulting from a single intake were calculated from the retention equations. From the results it could be concluded that most intakes of radioactive materials encountered in practice would give trivial doses of radiation to the body or critical organ; therefore it is not necessary to estimate radiation doses unless the uptake of radionuclide exceeds some prescribed Investigation Level (I.L.). The I.L.'s suggested by the Task Group were uptakes giving a dose commitment equal to one-twentieth of the annual dose limit.

For health surveillance, the Task Group also gave Derived Investigation Levels (D.I.L.'s) corresponding to the I.L.'s of about 30 radionuclides. These D.I.L.'s are the body content or daily excretion (usually in urine) corresponding to an uptake of 1 I.L. The D.I.L.'s are obviously functions of time after intake and their feasibility depends on the lower limit of estimation of the radionuclide. Information on these aspects are also given to help in the design of personnel monitoring programs (*14*).

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COMPARATIVE METABOLISM OF SELECTED RADIONUCLIDES IN ANIMALS

J. F. Stara, N. S. Nelson, R. J. Della Rosa, and *L. K. Bustad*

The magnitude of possible human population exposure to radionuclides resulting from nuclear energy processes is of primary interest in radiological health and safety. Comparative metabolism studies of the radionuclides in mammals are important because they provide basic information on deposition, distribution and turnover within mammalian organisms, thus presenting guidelines for their metabolic pathways in man; further, they enable a direct assessment of a potential population through data on tissue retention and concentration in animals involved in the human food chain. In addition, development of specific radionuclides and labeled pharmaceuticals for medical and research uses has further contributed to the population exposure and would, therefore, receive consideration.

Data on metabolism and effects of the radionuclides in humans are limited. Assessments of the hazard of the various radionuclides are more valid when values are collected for a number of animal species; however, extrapolation from one species to another is sometimes difficult. Even though there are general similarities in radionuclide behavior in mammals, often one or more of the species do not fit the general pattern. Interspecies differences are usually explained on the basis of genetic, physiological, and environmental factors. Differences are often magnified by experimental variables, such as the route of administration, age of animals, diet, size of dose, chemical form of the radionuclides, parameters measured, methods of data analyses, and others.

Since isotopes of related elements generally follow similar metabolic pathways, radionuclides of public health importance were selected and grouped by their respective chemical families. Criteria for selection included worldwide atmospheric contamination, general use in medicine and industry, contribution to the natural radiation environment, and radiotoxicity. Reported results supplemented by original work were compiled for the following radionuclides: radiocesium for the alkali metals; radiocalcium, radiostrontium, and radium for the alkaline earths; radiozinc for Group II of the transition elements; plutonium for the lanthanides and actinides: radioiodine for the halides; polonium and radiolead for Groups IV and VI of the transition elements; and radioruthenium for the transition metals.

Radiocesium (Alkali Metals)

Radiocesium, because of its entry into the food chain, is one of the biologically important components of fallout. Tracer studies with mice, rats, guinea pigs, dogs, monkeys, and man have shown that almost 100 percent of ingested radiocesium—like other alkali metals—is readily absorbed, the small intestine being the most active absorption site. Cesium 137 deposits in muscle tissues and may be secreted into the milk of animals used in human diets. Its turnover is quite rapid so that the tissue levels relate very well to the current dietary levels. The distribution of radiocesium is sufficiently uniform so that the referenced critical organ in the ICRP is the whole body. In most experiments, the highest concentration was found in skeletal muscle, followed by liver, spleen, bone, and testes.

The retention pattern in all animal species was expressed by three retention components: (1) a fast initial phase followed by (2) an intermediate phase, about 5 to 70 times longer, and (3) a final phase about twice as long as the intermediate phase. The biological half-life seems to be proportioned to the body weight. One notable exception is the case of ruminants, whose excretion of radiocesium is much more rapid than the monogastric species. The major route of excretion is via the urine; the U/F (Urine/Feces) ratio varies from 2 to 1 to 10 to 1 depending on species and dietary conditions. Various materials have been used to accelerate elimination of radiocesium from the body. To date, the greatest success has been obtained by increasing dietary potassium or sodium, using diuretic agents or certain inert sustances, such as vermiculite or Prussian Blue.

Radiostrontium (Alkaline Earth Metals)

Strontium, another important constituent of fallout, also appears in the food chain, especially in dairy products. Its metabolism has been studied in mice, rats, rabbits, dogs, swine, monkeys, cats, ruminants, and man. Strontium resembles calcium in general metabolism, and after ingestion between 5 to 50 percent is absorbed, depending on age, species, and diet. Excretion of skeletally deposited strontium is about equally divided between urine and feces in most species with a U/F ratio approaching unity. Dietary supplementation with sodium alginate substantially reduces the gastrointestinal absorption of strontium without significantly affecting that of calcium. The major site of deposition is in the skeleton, with 95 percent or more of the retained strontium localizing there; therefore, bone is considered the critical organ by the ICRP. Some strontium has also been reported to concentrate in the eye and cartilaginous tissues.

Retention of strontium, as of radium, can be expressed as a power function with reported values ranging from $0.45t^{-0.30}$ in rats to $0.73t^{-0.27}$ in humans. (In these equations, the unit of time (t) is in days). Values obtained for the long half-life ($T_{1/2}$) of strontium range from 400 to 1,800 days depending on species. Biological effects include changes in bone structure, osteosarcoma, carcinoma, and atypical myeloid leukemia. To confirm these, and possibly other effects, long-term studies are being carried out in several laboratories. Attempts to influence the reduction of body burden have utilized compounds to mobilize or replace bound strontium, chelates, and dietary manipulations, such as feeding of phosphates.

Radium 226 (Alkaline Earth Metals)

Radium, a naturally occurring radioelement, is found in varying concentrations throughout the human food chain. Studies of the distribution and metabolism of this divalent cation have been made in mice, rats, rabbits, dogs, swine, and man. Approximately 1 to 10 percent of ingested or injected radium has been reported to be absorbed. The primary organ of the deposition of ingested or injected radium is the skeleton, especially in areas of active bone mineralization. Relatively high concentrations also have been reported in cartilage, dark pigmented areas, and the thyroid. The ICRP lists bone as the critical organ. Excretion is primarily via the feces with the U/F ratios reported from 0.4 to 1 in the dog to about 0.02 to 1 in humans.

Retention of radium 226 is often expressed as a power function ranging from $0.60t^{-0.23}$ in the mouse to $0.54t^{-0.52}$ in humans, the change in slope probably indicating a species difference. Biological half-life ($T_{1/2}$) was estimated to be from 8,000 to 16,000 days. Biological effects are usually delayed and have included changes in bone structure and architecture, osteoporosis, osteosarcoma, increased tendency to fracture of ribs and of other bones, and degenerative nodules in the liver. Some cases of myeloid leukemia have been reported in association with high radium 226 burden. There is no reported effective treatment for radium poisoning.

Zinc 65 (Transition Elements, Group IIB)

Radiozinc is found primarily in reactor effluents; however, it can enter the food chain through contaminated irrigation water or marine life forms used as feed or food. Metabolism of zinc 65 has been studied in mice, rats, dogs, swine, and man. Absorption of ingested zinc is reported to be between 60 and 90 percent. Deposition is primarily in bone and muscle, although the liver and prostate also show high levels of ingested zinc. The ICRP criticial organ is the whole body because of the penetrating gamma radiation associated with this radionuclide. The principal route of elimination is via the feces. The reported U/F ratio ranges from 0.03 to 1.

Retention can be expressed as a slope of two exponentials; the initial component is almost 10 times steeper than the slow rate component. The biological half-life for the long component ranges from about 200 days in mice to nearly 1,000 days in man.

Plutonium 239 (Lanthanide-Actinide Elements)

Plutonium, an actinide, is associated with reactors and reactor fuel processing and releases from some weapons. Although it occurs in a mixture of four oxidation states, plutonium is usually employed in the tetravalent state in animal experimentation. Data on metabolism are available for the mouse, rat, dog, swine, and man. From 0.001 to 0.3 percent of ingested plutonium may be absorbed. Plutonium 239 is deposited primarily in the bone and the liver, where it is possibly associated with the reticuloendothelial system. The ICRP considers bone to be the critical organ. Plutonium is excreted primarily via the feces, with an initial U/F excretion ratio of 0.5 to 1, which increases later to about unity.

Initial retentions of 90 to 99 percent of injected plutonium 239 have been reported in the rat, dog, and man. Slopes of retention are extremely flat, of the order of −0.01 to −0.04 on log-log coordinates. Effects usually appear after a period of 3 or 4 years. The reported effects include changes in the structure and architecture of bones, damage to bone marrow, increased incidence of rib fractures, osteogenic sarcomas, degenerative liver nodules, and myeloid metaplasia in the liver, spleen, and lymph nodes. Suggested treatment for reducing body burdens include chelation, such as DTPA (diethylenetriamine pentaacetic acid), although EDTA (ethlyenediamine tetraacetic acid), and zirconium citrate have been used.

Lead 210 and Polonium 210 (Transitional Elements, Groups IV and VI)

Exposure to these radionuclides may occur both by inhalation and ingestion. Metabolism of lead and polonium has been studied in the mouse, rat, dog, and cat. Recent reports suggest that the discrepancy between observed metabolic behavior of polonium, particularly in soft tissues and the ICRP model, may be related to the particular chemical form in which the dietary polonium occurring in the environment eventually enters the body. The effect of chemical state has been demonstrated in rats. The concentration of polonium in the liver, lung, and the spleen of the rat was noticeably higher when the radionuclide was administered in neutral solution than when administered as a citrate. The absorption of ingested polonium and lead is reported to be 5 and 8 percent, respectively. Reported U/F ratios in rats vary from 0.03 to 0.1 for polonium after oral administration, and 0.2 for lead after oral administration.

The retention pattern of polonium 210 in the rat was described by a rapid phase with an effective half-life of approximately 30 days, and a slower phase with an effective half-life of 60 to 100 days. The two components reflect the turnover in various organ systems. Relatively high concentrations of lead 210 and polonium 210 were observed in organs of arctic caribou and reindeer, which serve as the basic diet for some Eskimos. In human bone samples, the concentration of lead 210 ranged from 2 pCi per gram to 10 pCi per gram of bone. The concentration of polonoium 210 in meat of the arctic animals ranged from 35 pCi per kilogram to over 500 pCi per kilogram. One report indicated that polonium 210 approximately equaled plutonium 239 in shortening the life span of mice and rats and was five times more effective than radium 226. A high-body burden in rats has resulted in generalized arteriosclerosis with secondary atrophy of organs.

Iodine 131 (Halides)

Radioiodine is a common contaminant from nuclear weapons and appears in high inventory in operating reactors. Human exposures may result from contamination of the food chain (chiefly milk) and from therapeutic or diagnostic uses in nuclear medicine. Iodine metabolism has been studied in rats, mice, guinea pigs, dogs, rabbits, swine, ruminants, and man. Absorption of iodine in monogastric animals approaches 100 percent. From 15 to 40 percent of an administered dose may be concentrated in the thyroid, which is the ICRP critical organ. In most experimental animals, iodine 131 is primarily excreted in the urine; however, considerable amounts of radioiodine appeared in the feces of rats and ruminants. The range of U/F ratios varies from 27:1 in man to unity in ruminants. Retention may be satisfactorily expressed by two exponentials: one with a very steep slope, the other much shallower. The reported biological half-lives for thyroidal iodine 131 varies from 4 days in the rat to over 100 days in man. Reported biological effects include histopathological changes in the thyroid and resultant hypothyroidism, as well as thyroid neoplasia. No one treatment to reduce body burden has been universally accepted, although several agents including a combination of injections of potassium perchlorate followed by thyroid stimulating hormone have been used. Sodium iodide or potassium iodide may be used to reduce thyroidal uptake if given shortly after the time of exposure.

Ruthenium 106 (Transition Metals)

Radioruthenium may enter the biosphere from certain discharges of reactor fuel reprocessing plants or from fallout. Absorption following ingestion is relatively low, with a recorded range of 1.5 to 18 percent. The highest absorption was recently reported for the nitrosyl ruthenium compounds found in reactor fuel reprocessing plants. The organs with the highest concentration, with the exception of the GI tract, were kidney, liver, and bone. The ICRP critical organ is the large intestine. Incorporation of radioruthenium into the wall of the small intestine gives rise to increased isotopic concentration in this tissue; the GI tract therefore receives a radiation dose higher than that resulting from the relatively rapid passage of the contents alone. The turnover of absorbed radioruthenium is quite rapid. Retention of ruthenium in most animals can be expressed by a two exponential function, with the longer phase about 15 to 20 times slower than the initial phase.

I would like to summarize this paper with only one statement taken from one of Dr. Cronkite's publications: "extrapolation of animal data to man are difficult and sometimes inaccurate; however, not to extrapolate presents a much greater risk."

GENETIC HAZARDS OF IONIZING RADIATION

William J. Schull

Twenty years ago mankind was unceremoniously thrust into a new, and atomic age. The circumstances that surrounded this change, one as potentially important to his future as the introduction of agriculture, were hardly auspicious. The world was engaged in its greatest war, and it was to be expected, therefore, that the first use of nuclear energy would be directed toward the prosecution of that war. This unfortunate association colored and has continued to color the attitudes of many with regard to man's potential to use nuclear energy constructively, but this viewpoint notwithstanding, it should have been apparent to all that inherent in this newly tapped source of energy was a capacity to build that was unprecedented. Unfortunately, existing knowledge ill equipped us to cope with the biologic, social, and economic problems presented by this new force. Now two decades later, we are much more knowledgeable with respect to these problems, but we live no more easily with our atomic handmaiden. Why? Wherein lie our fears? Do they stem in large measure from a general inability to cast the hazards as well as the benefits in a frame of reference meaningful to the individual? What do we know about the damage accruing to mankind as a consequence of increasing exposure to ionizing radiations? What guidelines to conduct can be set?

So extensive now are the data it can be asserted without qualification that the gentic damage, which accrues to a population from exposure to ionizing radiation, will be directly proportional to that exposure. This damage will assume the form of an increased burden of "point" or gene mutations and chromosomal abnormalities. The former will presumably vary in number with radiation intensity, the cell stage at the time of exposure, and, of course, the total dose. These mutations will, in general, be harmful in the sense that they will impinge on the reproductive fitness of the bearer either through diminished fertility or enhance risk of death, or both. They may manifest themselves in a variety of ways: for example, as an increased incidence of congenital defect, an elevation in infantile and juvenile mortality, an altered sex ratio, or a change in rates of growth and development.

Radiation-induced chromosomal changes may or may not be incompatible with survival, but in the aggregate they are expected to increase nonlinearly with dose. Since both loss and gain of chromosomes (through nondisjunction) are possible, it is reasonable to suppose that such syndromes as Down's, Klinefelter's, and Turner's will increase in frequency with increasing exposure, but the extent of this increase is uncertain for the dose-effect relationships for these changes are not presently known. We may also surmise that an increase in miscarried foetuses will occur since a substantial fraction of spontaneous abortions are, even under normal circumstances, associated with chromosomal abnormalities. Unfortunately, relatively little is known of the mechanism of induction of chromosomal anomalies in man, and even less about the dynamics of cell populations that determine the spread and persistence of a karyotypically abnormal cell. We cannot, therefore, begin to plumb all of the implications to a population of exposure to some given number of roentgens of irradiation.

It should be patent from the foregoing remarks that a qualitative assessment of the risks to man is even now possible, but a meaningful quantitative appraisal continues to elude us. The reason is obvious. No end of experimental studies of the mouse, Drosophila, or other laboratory animals, essential though they may be to a balanced view of the radiation hazard, can provide generally acceptable estimates of the radiosensitivity of human genes. This latter information can only be gleaned from further observations on man, and these are both extremely difficult to obtain and to assess. Much of the information now at hand stems from studies on the offspring of persons irradiated for some underlying disease, the effects of which may have been confounded with the radiation damage so as to obscure a real genetic effect or conceivably to create a spurious one. The only large, relatively uncomplicated study remains that of the children of the survivors of the atomic bombings of Hiroshima and Nagasaki. Clinical studies of those children born in these cities in the years 1948–53 failed to reveal significant differences in the frequencies of congenital defect, fetal and infantile mortality, birthweight or growth and development ascribable to parental radiation. The sex ratio did, however, appear to be significantly altered: a finding seemingly not corroborated by more recent observations. Lately there has been reported the results of a continuing cohort-type study of survival among these children. At 9 years of risk of death, on the average, no significant variation in mortality unequivocally attributable to parental radiation has emerged, and it seems unlikely, therefore, that mortality prior to maturity will be shown to be a function of parental exposure in either Hiroshima or Nagasaki.

These newer findings render it unlikely that the minimal doubling dose for mutations in man is less than 50 roentgens for radiation of the type emitted by an atomic bombing and for mutations of the kind resulting in early death in the first post-bomb generation. The doubling dose may, in fact, be more nearly of the order of 100 roentgens. Be this as it may, in the face of the uncertainties associated with our present knowledge and the necessity to lean so heavily on experimental observations on infrahuman forms, rigid guidelines seem premature. At present, the only meaningful guide to conduct is to reduce exposures to the lowest possible levels consonant with health and safety, both personal and national.

HEMATOLOGICAL EFFECTS OF RADIATION

John F. Loutit

The chief committees and commissions now determining our lives have long recognized the sensitivity of the hemopoietic tissues to radiation. This derives from two types of experience: (1) accidents and massive acute doses of radiation and (2) chronic exposure to lower doses. In each case the hemopoietic tissues rate high in terms of radiological sensitivity, and one of the means of determining effects of radiation has been, from the beginning of radiological history, the examination of the blood.

The Acute Massive Exposure

There are several approximate numbers to consider. A whole-body exposure of 10,000 rems (a really clobbering dose) will cause death in most experimental mammals and man within 1 to 2 days. This is always called the nervous system mode of death, but it now seems that the cardiovascular system is probably equally affected. Doses of the order of 1,000 rems will allow survival for perhaps 3 or 4 days. This form of death is usualy referred to as gastrointestinal. Doses of about 400 rems, give or take a bit, cause death of experimental mice in about 10 to 14 days; in man, as we have heard this morning, the interval is rather longer—several weeks—and this form is always known as hemopoietic tissue death.

The meaning of this is not that the central nervous system is more sensitive than the gut, which is more sensitive than the marrow, but rather, if you destroy, anatomically or functionally, tissues in the central nervous or cardiovascular systems, then such damage allows survival only for a day or so. For the gut, comparable damage allows a 4-day survival, but complete destruction of the hemopoietic tissues does allow survival for 10 to 14 days. The value of 400 rems as a lethal dose for the hemopoietic tissue is a fairly good figure. Although there are no accredited observations on this point, it is known that in mammals investigated carefully the median lethal dose is within a factor of 2, somewhere between 400 and 800 rems. It is, therefore, highly probable that the median lethal dose for man, also a mammal, would fall into this very narrow band, narrow, that is, when compared with general toxicological experience with bacterial and chemical agents.

What happens in experimental animals when such a median lethal dose of radiation is given? What happens to the counts of the elements of the peripheral blood? The lymphocyte count falls immediately and extremely precipitately and, should clinical recovery occur, the restoration of the lymphocyte count is extremely slow. By contrast, the granulocyte count falls after a day or so, also to very low values, but recovers, if the animal recovers, considerably in advance of the lymphocytes. The rate of recovery of granulocytes may not be uniform. There may be undulations in the recovery curve. Platelet count falls rather later than the granulocytes but recovers more uniformly. Finally the red cell count is well maintained for a considerable period of time and may not even be substantially reduced at the time of death; however, it may fall precipitately from hemorrhage because of lack of platelets.

The post-irradiation changes in value of these blood elements were formerly taken as indicators of the average life spans of these particular elements in the circulation. This postulated that the curve was entirely dependent on cutting off lymphocyte production. With the failure of production, the average life span of the lymphocyte was only a few hours. We now know that this is not so. Rather, the lymphocytes are particularly radiosensitive to a form of destruction and death in the interphase of mitosis. You do not have to irradiate the whole animal and the hemopoietic tissues in order to obtain this picture. It is now well known that if you exteriorise a part of the circulation and irradiate the blood in its extracorporeal circulation, you will get a similar fall in lymphocytes. The kinetics of this particular phenomenon do not represent lymphocyte production or even the life span in the blood. Probably the curves for granulocytes and platelets do bear some reasonable relationship to their average life spans in the peripheral blood. The half-life of the red cell is well known from other sorts of experiments to be very long.

How useful are such curves? In the first place, they are not uniformly related to dose. There is no linear relationship between dose and the lymphocyte count. This is one of the empirical examples of a threshold. You have to give a substantial dose of radiation before you can get any statistical depression of lymphocytes, or of any of the other elements, but once the dose is raised to a level that does give a significant result then the progression is very rapid. Because of this rapid progression, the test is insensitive for dosimetric purposes.

Clinically, the platelet count can be a very significant measure for determining whether recovery or death is going to occur. If the platelet count in experimental animals begins to rise after reaching low values, this is a most favorable prognostic sign and practically all the animals that pull out of this deep depression soon recover satisfactorily.

I mentioned that the lymphocytes die in interphase, but most of the deaths of cells in the hemopoietic tissues are presumably due to the consequence of mitosis. This has been the subject of a good deal of investigation over recent years. It appears that the sensitivities of most cells to mitotic death are very much the same. Something of the order of 100 rems is usually sufficient to produce a 50-percent mortality.

Let us now examine recovery. At one stage, 10 or more years ago, it was reckoned that this was due to humoral agents that stimulated the recovery of the surviving stem cells of the blood-forming tissues. We now know from our own experiments with animals that recovery does occur from stem cells, and that stem cells can be transferred artifically. One can facilitate recovery in the case either of sublethal or lethal doses of radiation when the number of surviving cells is too small for recovery to be effective in the available time. Recovery is possible by giving intravenously suspensions of hemopoietic tissue containing the stem cells. This is a clinically satisfactory procedure in mice, and probably in man, and it has proven to be a useful tool for fundamental research.

Till and McCulloch, in Toronto, have made remarkable use of their observations of the spleen during recovery. The normal spleen of various strains of mice weighs roughly 80 to 100 milligrams. After what is normally a lethal dose of radiation, there is atrophy of all tissues of the spleen, both the lymphoid follicles and the aggregations of myeloid cells in the red pulp, and the spleen is reduced to about one-half of its normal size. If a lethally irradiated mouse is given intravenously a marginally effective does of hemopoietic cells, then after 8 to 10 days one observes a few circumscribed nodules on the surface of this atrophic spleen. Till and McCulloch have shown to everyone's satisfaction that these nodules are localized foci of hemopoietic cells. Most are usually erythropoietic in character, but some are granulopoietic and a few of them are characterized as giant-celled platelet-producers. They have shown that each of the nodules is a clone arising from a single stem cell; furthermore, many of these clones can be shown to contain stem cells that can produce further clones in another recipient. An erythropoietic colony may produce further stem cells, which in the new test animal may produce granulopoietic colonies; therefore, through this means, we are learning something about the cellular processes of hemopoiesis.

Previously our information on hemopoiesis was derived almost entirely from histological studies and the subjective interpretation thereof. Rightly, our fathers deduced that the bone marrow was the hemopoietic tissue that produced the erythrocytes and granulocytes of the peripheral blood. By observation and deduction, they inferred that these definitive cells came from intermediate cells, normoblasts, and myelocytes, which in turn were derived from even more primitive cells that we can call promonoblasts and myeloblasts. There has long been the open question whether these were the ultimate stem cells or whether these promonoblasts and myeloblasts were derived from a common stem cell, which under the appropriate conditions was determined to the one or the other line. We now know from the experiment just described that there must be a common stem cell. It was formerly claimed that if there were a common stem cell, it must come from the reticuloendothelium system in the bone marrow. At the present time, one would very much doubt the classical histological interpretation. Even under the most extreme conditions, after lethal irradiation, there is no evidence that these cells are stimulated into mitotic activity.

The ultimate marrow stem cell we cannot yet identify. The marrow is comprised of cells identifiable as to erythropoietic and granulopoietic provenance, but in additon has quite a substantial population of what appears to be small lymphocytes and other cells of lymphoid morphology, but the nature of these lymphocytes and transitional forms has long been a subject for discussion. Professor Yoffey in Bristol for many years has studied these small lymphocytes and described forms intermediate between them and typical blast cells. On this basis they could be stem cells; however, Professor Osmond, formerly of Bristol, and now McGill, has produced with tritiated thymidine compelling evidence that the bulk of these small lymphocytes are produced in the marrow and are turned over with great rapidity. In my opinion, they are a product, not a source, of marrow, and marrow can be considered as a major producer of lymphocytes as well as red cells, granulocytes, and platelets for the peripheral blood.

Chronic Exposure

I can only refer briefly to effects on hemopoietic tissues of chronic irradiation. About 25 years ago, one used the standard blood counts as a biological dosimeter. Provided the numbers of the leukocytes and the characteristics of each class were normal, it was maintained that the dose of radiation was tolerable. It is now known that this was misleading. The presence of abnormal types of cells in the peripheral blood was almost certainly the warning sign of either marrow hypoplasia or even marrow malignant transformation; that is, leukemia. The consensus today is that we must control chronic exposure to radiation not by means of the classical blood count, but by the much more accurate means of physical dosimetry; moreover, what we are aiming at is to prevent, as far as is practicable, the development of leukemia or malignant disease of the blood-forming tissues. There are now observations on several series of human subjects: those exposed acutely and uniquely at Hiroshima and Nagasaki to ionizing radiation; those exposed acutely but repeatedly to radiotherapeutic procedures; and those exposed chronically and occupationally to ionizing radiation; for example, radiologists. From each of these human populations, there are data on the incidence of leukemia that can be related to some measure of dose these populations received. Given that the incidence of leukemia and total dose of radiation are linearly related, which is an acceptable but probably a pessimistic assumption, one can deduce for any dose permitted for occupational exposure what the incidence of leukemia will be as a possible outcome of these circumstances.

THE EFFECTS OF RADIATION ON BONE

Webster S. S. Jee

Both dysplasia and neoplasia are frequent consequences of irradiation of the skeleton. Dysplasia of bone following irradiation is not the chief hazard because the induction of bone neoplasia occurs at lower dose levels than those causing dysplasia. Also, contrary to earlier reports, radiation induced bone dysplasia need not precede the formation of bone neoplasia.

The most efficient bone cancer inductors are the alpha-emitting bone-seeking radionuclides. The essential hazard from the deposition of radionuclides in bone is the occurrence of osteosarcoma because of irradiation of the osteogenic precursor cells and the occurrence of squamous cell carcinoma in epithelium closely applied to bone (paranasal or mastoid carcinoma).

The study at the University of Utah under Professor T. F. Dougherty was established in 1950 to provide additional data on the relative toxicities of bone-seekers to radium in beagles. Radiation-induced osteosarcomas were present in 147 of 275 radioactive beagles dying as of June 1967. Only four squamous cell carcinomas have occurred in the same population. These dogs received radionuclide in a single intravenous injection in citrate solution when about 1.4 years old. The average values for the osteosarcoma dogs in the lowest injection levels at which the neoplasm has occurred are given in table 1.

Radium 226, plutonium 239, radium 228, and thorium 228, primarily alpha-emitting radionuclides, produced bone cancer at dose rates 11 to 18 times those corresponding to ICRP maximum permissible body burden for radiation workers. This ratio in the case of the beta-particle dose from strontium 90 was found to be even greater and induced osteosarcomas at an average dose rate of 530 times the per-

Table 1. ***Average values for osteosarcoma dogs in the lowest injection levels at which the neoplasm has occurred***

Radionuclide	Injected (μCi/kg)	Osteosarcoma dogs/ dead dogs	Years, injected to osteosarcoma	Rads to skeleton at death	Average rads per year	Dose-rate/ human MPD
Radium 226	0. 15	1/4	11. 3	490	44	15
Plutonium 239	. 016	4/10	9. 9	86	9	18
Radium 228	. 05	1/4	8. 7	306	35	11
Thorium 228	. 015	2/4	8. 8	130	15	20
Strontium 90	98	6/14	4. 1	11, 400	2, 800	530

missible rate. It is probable that osteosarcomas may occur in beagles at even lower dose levels and longer survival times.

Comparing the lowest injected dose levels that caused more than one osteosarcoma, RBE values relative to radium 226=1 are: plutonium 239=6; radium 228=3; thorium 228=14; and strontium 90=0.6.

Comparing the average skeletal dose rates that caused osteosarcomas at 8 years after injection, RBE values relative to radium 226=1 are: plutonium 239=10; radium 228=2.5; thorium 228=6; and strontium 90=0.1.

Differences in Relative Biological Effectiveness can be related to the chemical and physical (ranges and types of radiation) properties of the radionuclides and their local sites of deposition.

The alkaline-earth radionuclides—radium 226, radium 228, and strontium 90—deposit in sites identical to calcium. These radionuclides deposit in intense concentrations, called hotspots, where new bone is forming at the time of injection and throughout the preexisting old bone as a lighter diffuse component; thus, in the case of the alpha-emitting radionuclides, most of the alpha particles emitted by the radionuclide and its daughters are absorbed by the bone mineral rather than cells. The actinide radionuclides—plutonium 239 and thorium 228—initially deposit on bone surfaces. Approximately one-half of their alpha particles bombard cells and the other one-half the mineral; thus, in the case of the actinide radionuclide, a larger volume of cells are at risk.

PART II: PREVENTIVE MEASURES

Chairman: James G. Terrill, Jr.

Preventive Measures in Radiological Health
James G. Terrill, Jr.

Methods To Reduce Radiation Exposure in Diagnostic Radiology
Raymond T. Moore and *Harold F. Stewart*

Radioactivity Hazards in Laboratory Techniques
Kenneth G. McNeill and *Joan E. Harrison*

Preventive Measures in the Atomic Energy Industry
D. W. S. Evans, *C. G. Stewart*, and *A. M. Marko*

Radioactivity Hazards in Exploitation of Natural Resources
Victor E. Archer

Preventive Measures in Exploitation of Natural Resources
Duncan A. Holaday

The Role of Marine Plants on Radiation Protection
Yositeru Nakamura

Education and Training for a Peaceful Nuclear World
Benjamin H. Bruckner

PREVENTIVE MEASURES IN RADIOLOGICAL HEALTH

James G. Terrill, Jr.

It is my privilege to participate in this International Conference on Guidelines to Radiological Health as a representative of one of its sponsors—the National Center for Radiological Health of the Public Health Service. We regard this event as an outstanding opportunity to promote understanding of some of the problems in radiological health and the urgency for solving them among scientists and the general public.

My assignment this morning is to discuss with you preventive measures in radiological health. I am conscious of the fact that this subject will be covered quite comprehensively during this conference. I shall endeavor to confine my talk to those aspects that may not be reported in presentations at this and other conference sessions, and will be related to Public Health Service activities now being conducted by the National Center for Radiological Health.

The development of preventive measures in radiological health has become one of the great concerns of our time. We either must find better ways to protect the public's health against the hazards of radiation or relinquish prospects for outstanding progress in the application of the radiological and nuclear sciences in meeting human needs.

It is clear today that man is improving his ability to use radiation and nuclear energy. Because of this progress, it is clear that radiological health problems have increased markedly since the day when the primary concern was radioactive fallout.

We dare not assume that there will be no escalation of nuclear weapons testing. If so, they will again become a major public health concern. On the contrary, we must maintain the highest levels of efficiency in our environmental surveillance systems. The basic preventive measures are totally dependent on these surveillance systems, particularly in the case of such radioactive isotopes as iodine 131.

Unless we enter a new period of large-scale atmospheric testing of nuclear weapons, peaceful applications of nuclear energy will constitute the major source of potential population exposure to radiation. Nuclear energy, as most of you know, is rapidly becoming competitive with coal for the generation of electric power. The present estimate is that by 1980—just 13 years from now—the output of nuclear plants will comprise about 25 percent of the total U.S. electric power production.

At the present time diagnostic x rays represent the largest single manmade source of radiation reaching the U.S. population. This may be true also for Canada and some other countries. In many of the developed nations, electronic products—some with a high potential for hazardous radiation emission—are being manufactured in increasing numbers and sophistication and for an ever-widening variety of uses.

Generally speaking, circumstances for the control of radiation hazards are more favorable in industry than in the home. Partially for this reason, all of us with radiological health responsibilities must be especially concerned about the advent of electronic home appliances. Many types of electronic products, including color television sets, already are in use in households throughout the countries. Certain color television receivers have been closely associated with the emission of x rays at rates potentially hazardous for human health.

The story of x-radiation emission from approximately 100,000 General Electric large-screen color television sets is well known to all of you. The correction and modification of these defective receivers is an example of the influence a public agency can have to help remedy a situation when it lacks authority to act.

One of our first steps was to alert the public to what we knew about the situation. We then undertook our own evaluation of the problem through tests in our own laboratories and with data collected at our request by the Electronic Industries Association (U.S.A.). As soon as sufficient data were available, another statement was issued. This called attention to the fact that some 9,000 potentially hazardous sets were still uncorrected. The statement also made public some of our data.

Meanwhile, the General Electric Co. redoubled its efforts to locate and correct additional sets. Local and State health authorities and our regional representatives collaborated in this work.

I think the greatest concern at the moment is that some industry officials know little about radiation, or the people in the company who know something about radiation are out of contact with the people who are building television sets. I think in the large companies this is certainly the case. You have people working at General Electric who are quite knowledgeable about x rays, but they are out of contact with the people who are building the television equipment. A great deal of work needs to be done in this area to increase our level of understanding of radiation generation, exposure, and effects. Much more needs to be done in, say, medical x rays and radiation related to the atomic energy industry. We already have quite a bit of information, but by this I do not mean we have all the answers, and some of the other presentations will indicate this.

Continuing expansion of applications of radiation and nuclear energy has generated needs for public health protection in at least one other significant area. This is in the use of radioactive isotopes and other radionuclides in medical treatment and diagnosis and in research, agriculture, and industry. One example of the need for safeguards is the fact that for some years the United States has had losses of radiation sources, such as radium needles, and these have been occurring at the rate of more than 20 incidents annually.

Many of these losses have taken place during shipment. To help solve the problem, members of the staff of the National Center for Radiological Health have designed an interlocking shipping container. The plywood exterior of the container cannot be closed until the inner shield plug is inserted and locked in place.

This and some of the other work being done by the Center to minimize hazards in the use of radiation sources will be discussed during the presentation of a paper on "Industrial Exposure to Radiation," which is scheduled for one of tomorrow's sessions. The paper was prepared by Messrs. Villforth and Boggs and will be presented by Mr. Boggs.

The collection and assessment of the vast quantity of information on radiation hazards is a basic requirement if we are to protect the health of the people. The preventive capability of any radiological health program can never be any greater than its capability to estimate the distribution and magnitude of population exposure, to identify potential sources of radioactivity which may be released to the environment, to interpret environmental levels, and to delineate the pathways by which radiation enters the environment and the routes it takes to and within the human body. Without well-designed procedures and facilities for the collection and assessment of data and other information, it is impossible to establish realistic priorities for the assignment of available resources to develop and initiate preventive measures.

One of the best illustrations of the value of data collection and assessment in establishing radiological health priorities is provided by our 1964 survey of radiation exposure to the U.S. population attributable to medical use of x rays. The information obtained from a survey of 33,000 families positively identified diagnostic x rays as the largest single source of radiation reaching the people in my country.

One of the things that the study indicated is a need for a better system of collimation that could reduce the amount of exposure by about 50 percent and could be installed on medical x-ray apparatus, but in no way would interfere with medical practice. If this can be done, I think we will have taken a long step forward.

In an attempt to satisfy this need, since one of our functions is to reduce radiation danger in x rays, the National Center for Radiological Health developed three systems for reducing x-radiation exposure through electronic control of x-ray machine collimators, which Dr. Stewart will describe in detail. One of these systems has been in use for more than 3 months at the Public Health Service's National Institute of Health, Bethesda, Md. Another has been installed for a collimator at Georgetown University Hospital in Washington, D.C.—I wanted to call particular attention to this work as an example of how public health people can move with certainty to correct a significant source of exposure once it has been positively identified.

It seems obvious that the present knowledge and technology, which has been effectively applied to improve health through the use of radiation, can also be applied to correctly assess and evaluate the significance of the health problems associated with exposure to radiation. This latter ability is surely no less critical and should be applied to the design and conduct of research programs to meet this great need. This is the need for knowledge to expand and strengthen our present capacity for preventing radiation damage to health.

In some areas of radiological health responsibility, the ability to assess can be translated directly into the ability to prevent: for example, it should be possible to run a nuclear-powered electrical generating plant without hazard, under normal conditions, if an accurate health evaluation has been made and faithfully reflected in the selection of the site, and in the design and operation of such features of the facility as equipment and procedures for effluent and waste management.

Much of the foundation for the present capability of the National Center for Radiological Health for overall radiation hazard assessment is represented by evaluations and studies of data obtained over a period of several years through operation of five environmental surveillance networks and supplementary surveillance projects. The networks regularly measure levels of radioactive nuclides, such as strontium 90, iodine 131, or cesium 137, in air and atmospheric precipitation; in samples from the total diet of selected population groups; in human bone; in pasteurized milk from major production and consumption areas in the Nation; and in bovine thyroids. Data from the networks, it should be pointed out, are evaluated on a continuing basis in relation to guides established by the Federal Council on Radiation, as to radionuclides and levels below which protective measures need not be instituted. The Council is comprised of representatives of agencies of the Federal Government concerned with various aspects of the radiological health problem.

The primary function of the networks and the surveillance projects is, of course, to provide data on which health-protective decisions may be predicated. Experience obtained from their operations and, especially, studies made of network data have led to some of our more significant findings with respect to health protection and, in fact, to the development of specific prevention capability.

To begin with, the network operation confirmed beyond question the importance of the pasture-cattle-milk pathway in the ingestion of radionuclides of strontium and iodine by man. Furthermore, through analyses of data from the Pasteurized Milk Networks, and particularly the Bovine Thyroid Networks, it has become possible to identify rises in iodine 131 levels in terms of specific milk-producing areas, counties, and even farms. In addition, the demonstrated significance of milk as a medium for radionuclide intakes by humans, particularly among growing children, stimulated the development of two processes for the removal of radioactive iodine and strontium from milk with efficiencies of more than 90 percent.

Before briefly discussing the processes, it should be noted that countermeasures other than radionuclide removal might be preferable under certain conditions of radioiodine or radiostrontium contamination in the production of fresh milk. The feeding of dairy cattle with uncontaminated feeds, or with feeds that have been stored long enough for iodine radioactivity to decay, would reduce the hazard. The use of dried whole milk also would provide some protection. Another protective action that might be feasible would be the diversion of iodine 131 contaminated milk to processed food products with fluid-milk requirements met through shipments of uncontaminated milk from other areas. Two countermeasures for radioactive iodine that have been given considerable study in recent years involve the addition of stable iodine to the diet or the medical administration of thyroid extract.

Irrespective of the availability of other countermeasures and the fact that radionuclide levels in milk are well within acceptable limits, it clearly is prudent to have available a system for processing milk for radioiodine and radiostrontium removal. One of the units in the system is a full-sized commercial fixed-bed ion exchange plant with a capacity for processing more than 100,000 pounds of milk in 8 hours. The other is a pilot plant with an 8-hour capacity of 7,000 pounds, which uses a moving-bed ion exchange process. Both facilities permit concurrent removal of iodine 131 and strontium 90 from milk. While no significant change occurs in the chemical composition of the milk, a slight difference in flavor has been noted. The commercial process can be used by the milk industry with existing plant personnel.

The moving-bed plant has been designed for transportation on a standard truck trailer into any area in event of a sudden radionuclide intrusion. This would permit fast action that must be taken in radioactive iodine removal, since more than half the acceptable human dose of this radionuclide will have been received if a week elapses before the initiation of countermeasures.

Consideration now is being given to mounting the full-scale fixed-bed plant on several trailers. It has been estimated that the strategic location of six to 12 standby mobile units would make it possible to place a plant in operation in any milkshed in the United States within 24 hours.

In no aspect of the problem of preventing radiation damage to health is data collection and assessment capability more greatly needed than in conjunction with the location, design, and operation of nuclear-fueled electric power generating plants. The National Center for Radiological Health begins to discharge responsibility for the health safety of these facilities months before construction begins. Much of this work is performed by means of intensive study of Design Safety Analysis Reports prepared by organizations that will own the projected facilities or by their contractors.

These reports analyze site suitability, inherent and engineered safeguards, and health protection adequacy, including arrangements for the prevention of exposure in the case of accidents. The Center's study primarily is to serve two functions. One is to detect whatever anomalies or specific technical difficulties our specialists believe may have health significance. These are called to the attention of the U.S. Atomic Energy Commission for correction. The other main purpose of the study of the safety analysis reports is to facilitate discharge of the Center's obligation to provide technical assistance to State authorities in their review of the adequacy of arrangements for health protection and in their surveillance of the facility after operations are begun.

The Center's reports evaluate:

1. The health-protection adequacy of operating procedures in terms of the site, waste handling and disposal systems, land contamination, and emergency action planning.
2. Possible consequences of normal and abnormal operation.
3. Calculations of dose estimates to persons living in the environs of the plant as a result of abnormal operations.
4. The effects of possible reconcentration of any radionuclides discharged to the environment under both normal and abnormal operating conditions.

The Center's health evaluation reports call attention to many kinds of potential hazards in the location and operation of nuclear plants; for example, calculations are presented to show that a dairy farm 2 miles north-northeast of the facility could experience an iodine 131 concentration in cow's milk in excess of the Federal Radiation Council's protective action guide of 100 pCi of iodine 131 per liter if the radionuclides were to constitute about 5.7 times 10^{-6}, or 0.00057 percent of the average gaseous activity expected to be released from the plant under normal operating conditions. In addition, calculations are submitted on the basis of the applicant's analysis of Maximum Credible Accident that show the thyroid dose of a 1-year-old child, could be in the range of 1,000 to 3,500 rems in the event of such an accident from drinking milk from this particular farm.

These calculations mean that local and State health authorities should conduct a survey to locate dairy cattle or dairy herds in the environs of the proposed facility as the first step toward formulation of a protective action plan. The calculations also mean that gaseous effluent from the plant stack must be monitored for radioactive iodine as well as for gross radioactivity. Furthermore, if the survey should show that no cattle are in or likely to be in the environment, consideration must be given to the possible contamination of other food-production operations.

Preparations have been made for surveillance and evaluation of such radiation as may result from an experiment to be conducted in western New Mexico next October to study the feasibility of using an underground nuclear explosion to increase the productivity of low-flow natural gas reservoirs. Baseline levels of radon 222 were obtained in 307 gas wells during 1965 in anticipation of this "Project Gasbuggy" blast. Success in the undertaking is expected to be followed by a comparable experiment and, ultimately, by a commercial-scale nuclear-blasting operation far below the surface of the ground in the general area of the Gasbuggy test. Evaluation of the environmental safety of the latter explosions and the gases that may be offered for commercial distribution would be conducted by the National Center for Radiological Health in cooperation with the Atomic Energy Commission.

One of the Center's studies of specific radionuclides as sources of potentially hazardous environmental radiation recently attracted national attention. Smoking machine tests of polonium 210 in tobacco showed that between 11 and 30 percent of the total tobacco content of the radionuclide, a suspected cancer producer, remained in the smoke. By autopsy, the lung, blood, and liver had been found to contain more polonium 210 among smokers than nonsmokers. Scientists in the Center's Southwestern Radiological Health Laboratory at Las Vegas, Nev. recently demonstrated that an ion exchange resin incorporated in a cigarette filter removed more than 90 percent of polonium 210 from smoke.

The Public Health Service, it should be emphasized, has no regulatory authority in radiological health. It cannot, for example, establish and enforce health standards for radiation-using equipment. It can work with State agencies in the development of such standards. But in achieving compliance, it now has no power other than that of persuasion. Yet, this power when collaboratively exercised by local, State, Federal, and private agencies sometimes has proved effective.

A good example of the effectiveness of persuasion is provided by the history of the use of fluoroscope machines for fitting shoes. Not many years ago, the use of this equipment in just about all parts of the country was subjecting uncounted numbers of shoe store customers, including children, and store employees to radiation at rates often greatly in excess of acceptable standards. Levels as high as 97,200 milliroentgens an hour, for instance, were found in one location by one State agency. Also, during this period, between 30,000 and 40,000 shoe store workers were being exposed chronically to unnecessary radiation. Today, owing in great part to educational efforts by public and private organizations, fluoroscopic shoe-fitting devices are regulated in all States and the District of Columbia.

The Radiological Health Center plans further investigations to obtain a better definition of the movement and dispersion of the more important radioactive contaminants from sources to ultimate disposition in man. The objective is to determine critical points in transmission pathways where preventive measures are likely to be most effective. We believe that conventional public health practices for controlling disease by controlling the carrying agent or vector may be adapted to some aspects of the problem of radiation control.

The Center has underway and is supporting research directed toward the identification of animal feed additives that may reduce materially the animal uptake of radioactive contaminants, especially those additives that may affect the secretion of radionuclides into milk. Encouraging success already has been achieved, as many of you may know, in reducing the uptake of radioactive elements by dairy animals, and we hope we may be able to demonstrate procedures for accomplishing this before very long.

It is now known that alginates originating in certain seaweed species may reduce the uptake of strontium while permitting the incorporation of calcium in mammalian skeletons. Collaborative research on this subject is being conducted by a contract with McGill University and in laboratories of the Radiological Health Center. Feeding experiments are to be undertaken to see if effects demonstrated in laboratory animals can be replicated in dairy herds. The importance of this work is underscored, as you are probably aware, by the fact that some gelatins consumed by humans contain alginates as a basic ingredient.

The subject of radiological health education is to be covered at this conference session in a presentation by Dr. Bruckner, another of my associates in the National Center for Radiological Health, so I shall not dwell on the urgency of balanced national radiological health education. I would point out, however, that shortages of trained radiology personnel in my country are still critical. There is a great need, moreover, for a broad understanding of radiological health requirements in any democratic society where the population at large must understand and support policy decisions that weigh health hazards against opportunities for progress through the use of radiation and nuclear energy.

We in public health and members of our societies generally must understand that drastic measures to achieve radiation protection may create an even more serious health hazard; for example, it might be preferable to accept a given radiation exposure than to risk a possibly greater hazard in trying to control the food supplies for a large population.

Measures for prevention in radiological health must be assessed in relation to many criteria. These include effectiveness. feasibility, and, as I just indicated, the consequences for overall public health.

No one wishes to risk health impairment as a price for progress in the radiological and nuclear sciences. What we really want is better health plus progress in radiology and nucleonics. Achievement of that result would have to be ranked as a major contribution to the health and well being of future generations of our countrymen.

METHODS TO REDUCE RADIATION EXPOSURE IN DIAGNOSTIC RADIOLOGY

Raymond T. Moore and *Harold F. Stewart*

The present state of x-ray protection is the result of more than 70 years of study, starting with Roentgen's discovery of x rays in 1895. Initially, the aim in protective measures in diagnostic radiology was to avoid immediate radiation damage to the skin. It was soon recognized that radiation effects were also cumulative. As a result, measures were instituted to further reduce exposure to operators and patients, in an attempt to minimize late radiation damage. In the years since the wide-scale use of atomic energy, much attention has been given to population-wide radiation exposure levels, largely because of the genetic risk. The 60 million medical diagnostic x-ray examinations each year in the United States have been identified as a major source of manmade radiation reaching the population; thus, the need for protection from this source of exposure, both patients and operators, is now well recognized.

The means of minimizing exposure from diagnostic medical radiology can, in general, be divided into three categories: (1) equipment design, (2) operating techniques, and (3) judgment. This paper will include examples of preventive measures in the first two categories that can be employed to reduce exposure while maintaining acceptable diagnostic quality.

Reduction of Exposure Through Equipment Design

The 1964 Population Exposure Study by the U.S. Public Health Service identified excessive beam size as the principal cause of unnecessary radiation exposure in diagnostic radiography. The study indicated that beam size was more than twice the film size in 26 percent of such exposures (*1*). Inspection programs by States have also indicated that excessive beam size is a most important factor contributing to unnecessary radiation exposure. The inspection program in New York City revealed that in chest radiography, where a 14- by 17-inch film is used, beam size exceeded 33 inches in one-half of the examinations (*2*). Epp, Weiss, and Laughlin (*3*) reported that if a 33-inch beam is positioned so as to directly irradiate the ovaries or the testes the resulting gonadal exposures are respectively 80 or 400 times higher than with a field size limited to the film size.

By confining the beam to the smallest area practicable, reductions in exposure to the skin, total tissue volume, and gonads of the patient may be achieved. With this in mind, a project was started at the X-ray Exposure Control Laboratory of the National Center for Radiological Health to develop an automative x-ray beam collimating system for use in routine diagnostic procedures. Our objective was to develop a collimation system that would confine the beam to the film for work done in the Bucky tray and in the chest cassette. The previously mentioned U.S. Public Health Service study (*1*) indicated that about 59 percent of all nondental radiographic examinations involved the chest, 9 percent the upper abdomen, and 13 percent the lower abdomen. Since all of these examinations use either the chest cassette or the Bucky tray, an automatic collimating system that would automatically adjust the area of the x-ray beam to the film size would account for approximately 80 percent of the exposures in diagnostic radiology. For the remaining examination, performed on the table top, the operator could manually select the field size.

The automatic collimating system developed by NCRH consists of four basic mechanisms: (1) a cassette size detector, (2) a motorized x-ray collimator, (3) a pair of servoamplifiers, and (4) a source-to-Bucky plane distance compensating unit. The cassette size detector is a modified Bucky tray for a radiographic machine. When a cassette is placed in the Bucky tray, switches corresponding to both dimensions of the cassette are actuated and send two electrical signals, proportional to the cassette dimensions, to the servoamplifiers. In addition, the motorized collimator sends the servoamplifiers a set of signals indicating the position of the collimator shutter.

The signals from the collimator and Bucky tray are compared; the amplified difference signal then actuates the motors, which drive the shutters of the collimator in the direction that will reduce the difference signal. The difference signal will become zero when the shutters reach the position defined by the cassette in use, at which point the motors stops. When the cassette is removed, the shutters close completely.

Adjustment of the shutter positions for changes in source-to-file distance is accomplished by a potentiometer which senses the source height, and consequently varies the voltage applied to the cassette size detecting unit. To adjust the system for chest x-ray exposures, a relay and a mercury switch are used. When the tube is rotated to the horizontal position, the mercury switch closes and actuates the relay, which disables the vertical compensating circuit. The system can be preset to produce the appropriate beam size for various preselected source-to-film distances. This prototype has been successfully tested in a hospital x-ray department.

Another example of equipment design that simplifies operation, while minimizing radiation exposure, is automatic exposure control. This refinement is employed in photofluorographic equipment and many other special purpose x-ray units now commercially available. Further research and development might well result in more general utilization of automatic exposure control. Some x-ray units now becoming commercially available utilize automatic exposure control in a machine with a fixed tube head, designed for certain routine radiographic procedures. These units eliminate manual adjustments demanded by general-purpose machines, thereby avoiding repeat films necessitated by poor beam alignment and/or incorrect adjustment of exposure control parameters.

Fluoroscopy is an example where the utilization of modern equipment can reduce patient exposure. Because fluoroscopy delivers a continuous exposure for a period of minutes, it potentially may result in larger amounts of radiation exposure to patients than any other medical diagnostic application. The use of an image intensifier will materially reduce the exposure rate required in fluoroscopic examinations. Utilizing other features of modern equipment to obtain the shortest possible exposure times and smallest practical field size can also reduce exposure. This may include utilizing spot films, cinefluorography, or a viedo tape recorder to record the examination for viewing later and further study. Other equipment design features for dose reduction include increased x-ray tube-to-patient distance and radiation protection shields around the periphery of the x-ray table.

Filtration of the primary x-ray beam is a means of reducing input radiation to patient without loss of the necessary exit radiation required to produce the film image. This exposure reduction is accomplished because the filter absorbs the soft relatively nonpentrating x-rays that would otherwise be absorbed in the body and not reach the film; thus, if these soft x-rays were not absorbed by the filter, they would be absorbed in the patient, increasing the patient dose without aiding in the production of a useful image. While filtration between the tube and the patient reduces exposure, filtration between the patient and the film increases the exposure because of the absorption of part of the useful beam that otherwise could be used in the production of an image on the film; thus, cassettes that have low absorption fronts can also reduce patient exposure.

Techniques for Radiation Dose Reduction

The goal of reducing unnecessary radiation dosage, while maintaining diagnostic quality, cannot be achieved by equipment design alone. Even with the best available equipment, radiation safety is largely dependent on its proper and conscientious use by competent operators concerned with minimizing unnecessary radiation exposure; for example, automatic collimation is accomplished by reference to the film size, but the beam size can be further reduced by the operator if the area of clinical interest is smaller than the film. Another example of radiation protection through proper technique is the use of gonadal shielding when the gonadal area must be in the primary beam.

According to the 1964 U.S. Public Health Service Population Exposure Study (*1*), the genetically significant dose to males was 4.4 times that received by females. That study also reported that, in the 15- to 29-year group, males received a 33-millirad average yearly gonadal dose compared to 7 millirads for females. As a result of these findings, the X-ray Exposure Control Laboratory of the National Center for Radiological Health conducted a laboratory and hospital study to evaluate the effectiveness and practicality of male gonadal shielding. The results of this study suggest that male gonadal shielding should be used routinely whenever males with child-producing potential receive primary beam radiation to the lower abdomen and pelvis.

An important means of reducing patient exposure is the use of fast films and screens. This is one of the most effective ways of accomplishing dose reduction in diagnostic radiology because it significantly reduces the amount of radiation required to produce a radiographic image. When using radiographic film, it is important to achieve full development of the film if the exposure to the patient is to be kept at a minimum level. This means that the film must be processed at a proper temperature in fresh developer for a sufficient time to bring about complete conversion of the reduced silver in the film emulsion. Overexposure occasioned by underdevelopment of x-ray film results in unnecessary increases in all types of patient exposure. Morgan and Chaney reported that unnecessary patient dosage may be reduced by as much as 40 percent by improvements in darkroom technique (*4*).

Improved control of patient dose may be achieved by equipping the x-ray unit with an integrating dose meter mounted so it intercepts the entire x-ray beam, usually at the exit portal of the collimator (*5, 6*). This type of monitoring provides the radiologist with dose indications for various procedures and techniques, enabling him to evaluate his operating practices and perform his diagnostic work under optimum conditions.

SUMMARY

Selected examples of dose reduction through equipment design and the utilization of proper techniques by well-trained, competent operators have been presented. These examples are not intended to be exhaustive, but merely to review past progress and give some indication of future trends.

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RADIOACTIVITY HAZARDS IN LABORATORY TECHNIQUES

Kenneth G. McNeill and *Joan E. Harrison*

The laboratory techniques involving radioactive hazards that will be discussed by me today are confined to diagnostic and other investigative procedures. To define my subject more closely, I should state that I intend to deal mainly with laboratory practices that are concerned with internal sources of radiation, and further I intend to consider only gamma rays. I should also make it clear that I do not intend to cover ground already well covered in this meeting, but I would like mainly to discuss changes that may be taking place in this matter of radioactive hazards in laboratory practice as a result of recent and fairly recent developments in technology.

I assume that the object of the use of radioisotopes in laboratory practice is to obtain biological, chemical, physical, or other information, but at the same time to keep radiation doses to individuals and to the general population at a low level—maximizing the information while minimizing the radiation hazard. Most commonly these two objectives are at variance with one another—more information can be obtained more quickly if the radiation dose is increased.

Particularly in the early days of the use of radioactive isotopes, the hazards were not properly appreciated, and at times radioactive material was used in a way which, from hindsight, seems somewhat indiscriminate. The effects of some such uses are still showing up, and I propose to come back to the matter of Thorotrast later on. Not only were the hazards unappreciated, but indeed the data on which proper calculations of dose to organs and to the whole body could be based were not available. I think it is fair to say that at present the hazards are appreciated, and that there is sufficient data available to make sensible calculations possible in most cases, however, this is a situation of comparatively recent occurrence. In the past much data were collected from animals, but the validity of using such data in the human situation is not obvious—there is the classic case of the biological half-life of cesium which is roughly five or 10 times higher in humans than it is in rats.

I should like first to put the matter of radiation hazards from typical radioisotope diagnostic procedures in some kind of perspective. To do so properly may well be considered to require a value judgment of the worth of various procedures compared to the risk of radiation damage, and very few of us are in a position to make such a judgment; however, it is possible to make estimates of the total dose being given to patients and then to the population at large.

Some estimate of the activity given to a patient in a typical procedure is required, then an estimate of the integrated dose received from this procedure, and then an estimate of the total dose received by the population from all procedures, with an extrapolation to future time. The ICRP Publication No. 9 suggests that from medical procedures the genetic dose is between 0.2 and 2 R, which is below the 5 R that ICRP considers a danger signal from all other manmade exposure. I think it is interesting to see how such a figure of 200 mR may be arrived at in terms of individual investigations. At one of the large hospitals in Toronto, the more common radioisotopic diagnostic procedures are iodine 131 uptake tests, brain scans using technetium 99, thyroid scans using iodine 131, and liver scans using gold 198. Typically in these procedures, doses in the region of 20 to 100 to 1,000 μCi are used, depending on the particular procedure. This gives rise to total radiation doses of the order of rads to the critical organ and perhaps an order of magnitude less to the whole body, that is, perhaps 200 milliroentgens. Currently at the Toronto General Hospital there are approximately 600 such tests being carried out every month, and if one assumes that multiplying by 50 will give the total dosage given in such tests over the whole of Canada, a figure of 70 kilorads per year is arrived at. This looks like a large figure, but when the figure is divided by the total population of 20 million, it gives an extremely small dose per year per person and results in about 100 mR per generation. As a result it doesn't appear that one has to worry about genetic effects resulting from such diagnostic tests. Of course, it is necessary to extrapolate this to the future, and again using figures from the Toronto General Hospital it would appear that the number of tests is increasing very rapidly—by a factor of more than 10 in 4 years. It can well be imagined that another factor of 10 increase may take place, and indeed could take place before one begins to become concerned about genetic effects, though with a factor of 100 one might begin to wonder.

The concern then is about doses to individuals, and although it is clear that the dosage received from ordinary diagnostic tests is small and that there is no cause for worry, yet there is no doubt that the correct procedure is to reduce the integrated doses to as great an extent as possible on the assumption that any radiation is bad. ICRP assumes a linear relationship between dose and risk of induction of malignancies because of lack of definite evidence to the contrary. This reduction of dose is particularly to be desired in situations that are of a laboratory nature, that is, when developing tests, a number of control subjects who do not need diagnostic tests from their own medical point of view is required.

Whole-Body Counters

One of the most obvious ways by which one can reduce the dose required for a given amount of information is by increasing the efficiency of the detecting system. If larger NaI crystals are used, the probability of detecting a given gamma-ray line is increased. Quantitatively, going from a ½-inch to a 3-inch-thick NaI crystal increases the probability of detection of a source of 1-MeV gamma radiation ray by a factor of about 10. This is not the only advantage; in addition there is an increased probability of the total energy of a gamma ray being absorbed, resulting in a greatly increased photopeak efficiency. Large NaI crystals are therefore favored for investigative work.

Unfortunately, the very fact that the large crystals have a high-detection efficiency means that they will see a high background from all sources, including cosmic radation, natural radioisotopes in building materials, and any accidental sources, unless they are well shielded. Almost complete thick lead shielding can be very helpful not only in reducing background but also in producing intense collimation in scanners for particular organs; however, for isotopes that are widely distributed, such collimation can be a disservice. It is in such cases that the whole-body counter (WBC) comes into its own. The WBC is a shielded device in which the source is the human body, and the source as well as the detector is within the shielding. This then provides 4π shielding of the crystal and maximum viewing of the source by the detector. Typically, the shielding so cuts down background that the major source of high-energy residual background is the potassium in the glass of the photomultiplier tube or impurity potassium in the NaI. Typically the natural potassium of the human body can be readily distinguished in a comparatively short space of time, from a few minutes to 30 minutes, depending on the size of the detecting system. This implies that a few nanocuries of a 100-percent gamma emitter in the body can be fairly readily detected and measured. It is of interest that the present (1967) body burden of cesium 137 from fallout is about 6 nanocuries, and this is the same order of magnitude as the effective gamma activity of potassium 40 in the body.

If a few nanocuries can be readily detected, it is clearly possible to use doses of microcuries or less in a diagnostic procedure rather than the tens of microcuries that are otherwise commonly employed. It also means that even with doses of microcuries, it is possible to follow the retention of radioisotopes in the body for comparatively long times even though the biological and/or radioactive half-lives are comparatively quite short; thus, it is possible to study the retention of an isotope such as strontium 85 for hundreds of days even though all but 10 percent is fairly rapidly excreted, and strontium 85 has a physical half-life of 65 days. As strontium 85 can act as a marker for calcium, one can essentially study calcium retention over long periods of time with initial burdens of only a few microcuries.

This matter of the direct measurement of the amount of retained radioisotope is one of the greatest uses of the WBC. Without the possibility of such a measurement, retention can only be inferred by calculation from excretion data. Such calculated information is likely to be highly in error after long times, because an attempt is being made to measure a retention of about 5 percent by subtracting an excretion of 95 percent, plus or minus some error, from the original 100 percent ingested. Being able to measure retentions properly means that biological decay constants can be measured properly, and the integrated doses produced as a result of initial intake of isotope can be calculated, a necessary calculation whose importance has been touched on before.

High-Resolution Detectors

One of the major advantages of NaI crystals over such earlier techniques as Geiger-Mueller counters is the ability to differentiate gamma rays from different nuclei. Although organic scintillators have this ability to some extent, NaI has a very much greater energy resolution. This ability seems at first sight to be unnecessary when radioisotopes are deliberately introduced into the body, because it should be known what activity exists. The use of radioisotopes in hospitals is becoming so widespread that it is not uncommon to find that persons with whom it is wished to carry out tests have already had, for example, an iodine uptake test. If it is known that the subject is "clean" and is to stay "clean," then full use can be made of the economy of plastic scintillators, and a very high-efficiency detection system can be set up at a relatively low cost. In modern steel room systems it is common practice for both NaI and organic scintillators to be available possibly in two separate rooms so that, as desirable, either a very high-efficiency or a high-resolution experiment can be carried out.

Modern technology has produced even higher energy resolution gamma detectors in the form of solid state germanium detectors that have been lithium drifted. Lithium-germanium detectors are usually small because of the difficulties in manufacturing them, and 5 cm^3 detectors are common. However, detectors of 40 cm^3 or more are now available commercially. Even with 40 cm^3 detectors it would appear at first sight that the efficiency for detection of gamma rays would be very low when compared to the efficiency for NaI crystals. A 5- by 5-inch NaI crystal, for instance, has a volume of 1,700 cm^3, 40 times that of a 40 cm^3 detector; however, the greater energy resolution of lithium-germanium detectors increases the effectiveness of detection. Typically a lithium-germanium detector has an energy resolution of a few kilovolts at an energy at which a NaI crystal has typically an energy resolution of 100 kilovolts. As a result, any peak sticks out far more sharply than is the case with a NaI crystal. Of course, not only is the peak narrower but it is much higher because the available counts have to be contracted into a much smaller energy interval. If we assume that with a NaI crystal the photopeak is 100 channels wide on some multichannel analyzer, and there are 10,000 counts in the photopeak in a certain time interval, then by a rough approximation there will be perhaps 200 counts in the peak channel sitting on a background of approximately 50 counts per channel. Perhaps this background is due to Comptons from other gamma rays or other sources. With a 40 cm^3 lithium-germanium detector under similar conditions, there may be 200 counts in the whole peak, but these will be spread over only perhaps three or four channels, and the counting rate in the top channel can well be approximately 100 sitting on a background of about one count per channel. This is comparable with the counting rate per channel in the NaI case while the peak-to-background ratio will be improved in the peak from a factor of 4 to a factor of 100. Of course, the lithium-germanium detector really comes into its own when there are a number of interfering isotopes in the body.

Short-Lived Isotopes

It is clear that if both biological and radioactive half-lives of an injected nuclide are of long duration (months or years) the total integrated dose given to a patient will be high. Correspondingly, if either the T_B or the T_R is short, the total dose is reduced for the same initial body burden. Particularly in the case of those techniques, such as thyroid tests, in which the total doses may be of the order of rads or tens of rads, attempts have been made to find substitutes for the iodine 131 commonly used. In the case cited, one is required to use iodine, but other isotopes of this element have shorter half-lives than the 8 days of iodine 131. Iodine 132, for instance, has a 2.3-hour half-life, and use has been made of this nuclide; however, the 2.3-hour T_R is so short that considerable difficulties arise in the easy use of it on a routine basis. Iodine 133 has a half-life of 21 hours, and would be easier to use than iodine 132, but it is of interest that it is now iodine 125, with a 60-day half-life, that is being used rather than iodine 132. Clearly T_R is not the only factor entering into the decision about the use of a particular nuclide. Availability is indeed one factor so far not mentioned, but the one I would like to stress is the decay scheme of the particular nuclide and the effect this has on dose.

Iodine 131 and iodine 132 both emit beta rays as well as the gamma rays which are detected. The betas have a relatively short range, on the order of a few hundred milligrams of tissue, and as a result give up all their energy in that distance, that is, in the organ which concentrates the isotope. The associated gamma rays have a much larger range, and either escape from the body or dissipate their energy in a large mass of tissue, reducing the dose. The main dose is from the betas. Iodine 125, on the other hand, has no beta emission since its decay is by K capture and only x rays (of about 30 keV) are emitted. For the same reason (that they decay mainly by K capture and therefore give out x rays and but few betas) xenon 133, technetium 99, and selenium 75 are being much employed at present in an attempt to keep down radiation doses.

There is considerable interest in such short-lived isotopes as oxygen 15 and nitrogen 13 that have half-lives of 2 minutes and 10 minutes, respectively. The reason for this interest is not the fact that they are short-lived and therefore give low radiation doses, but rather the fact that these are the longest-lived isotopes of these biologically interesting elements. If longer-lived isotopes were available, it is certain that they would be used despite the greater dose which would result.

Despite all the aforesaid, if one can use a short-lived isotope, it is clearly preferable. Fluorine 18 has been found to be of great value because of its short half-life (1.9 hours). It is a positron emitter, and therefore manifests itself by emitting two 0.51-MeV quanta in opposite directions, which enables localization of, for instance, intercranial lesions to be carried out by coincidence counting. The recommended amount of fluorine 18 is about 1 millicurie, giving a whole-body dose of 0.05 R compared with 0.42 R from 3 mCi of copper 64 or 1.8 R from 1.3 mCi of arsenic 74. Actually with 1.3 mCi of arsenic 74 (half-life—17 days) the kidney dose is approximately 7 R. If it is necessary to use arsenic, the use of arsenic 72, with a half-life of 26 hours and more positrons per disintegration, is preferable and reduces the whole-body dose by a factor of 3.

In Vivo Activation

A recent development in technique involves the production of radioisotopes inside the body in vivo by external beams of neutrons, neutrons produced either by a reactor or by the D–D or D–T reaction with an accelerator. On the face of it, this looks like a rather dangerous pursuit, but the workers in the field claim that when properly controlled the doses are no higher than with conventional radioisotope techniques.

At the Scottish University's Reactor Centre, following an idea of J. Lenihan of the West of Scotland Regional Hospital Board's Physics Department, the stable iodine contents of patients' thyroids are measured by counting the amount of 25-minute iodine 128 produced after exposure of the thyroid to a collimated slow neutron beam. Typically the patient lies over a 6- by 3-inch thermal neutron column and is irradiated for 5 minutes with a thermal neutron flux of 2×10^7 n/cm^2 per second. It might be noted that this flux is about 5×10^4 times the 40-hour whole-body exposure for occupational workers, but of course the exposure is for only about one six-thousandths of 13 weeks.

The iodine 128 0.46-MeV gamma-ray activity is counted with a NaI crystal and compared with the activity produced in a known quantity of iodine irradiated and counted under similar conditions. With the figures quoted, each milligram of iodine in the thyroid could be expected to give rise to about 100 disintegrations per second, or—in a normal thyroid—an activity of 20 nCi. This disintegration rate is readily measurable, but is clearly small compared with doses usually given and the short half-life makes the total dose negligible. The dose that causes concern is not the dose from internal radiation but from the direct dose from the neutrons. Even this, calculated from measurements, will be about 10 rems during the 5-minute irradiation, and adding this to the 2.5 R or so from gamma rays gives no more, in fact less, than the dose given by a standard iodine 131 thyroid uptake test.

Thorotrast

At the beginning of this talk I said that effects of the indiscriminate use of radioactive materials in earlier days are still showing up. The case of the radium dial painters is well known and will not be discussed here. Effects owing to thorium left in the body after thorotrast injection are less well known. Thorotrast is a colloidal solution of thorium dioxide, and was used in the period 1930–1960 as a contrast medium for radiography because of the high Z of the thorium. Even though less is known of the results of this injection than is true of the analogous radium cases, there is nevertheless a large corpus of information on patients, particularly in Portugal, who were given intravascular injections of about 4 to 6 grams of thorium. When given intravascularly, thorotrast is picked up by the reticuloendothelial system and remains in the body indefinitely, with most of it remaining in the liver and spleen. There is evidence of increased incidence of liver tumors, liver fibrosis, leukemia, and other blood disorders. The dose rate to the liver has been on the order of 10 rem per week over a period of 10 to 30 years in the Canadian cases we have looked at in Toronto.

One aspect of thorotrast that has received little attention so far is the results of the use of thorotrast in myelography for showing up details of the spinal column by x radiography. In the course of a wider study of thorotrast problems, we have now (1967) looked at 5 persons who had thorotrast myelograms. All five have acute arachnoiditis, although arachnoiditis is only rarely associated with other forms of myelography. In addition, the only other five patients who had thorotrast myelography, and of whom we have subsequent record, also have had arachnoiditis. Those that we have measured with the whole-body counter appeared to have significantly less thorium burden than do the arteriogram group of cases, probably because of the fact that after x radiography attempts were made to extract all possible dye from the spine. To make a proper calculation of the total dose received from all the daughters of the radioactive chain starting with thorium requires a knowledge of the excretion rates from the body of all the daughters, as well as a knowledge of the localization in the body of the alpha emitters. Although there is a fair knowledge of the appropriate washout factors for intravascular injection cases, there is less knowledge about the myelogram cases. Measurements at Toronto, however, indicate that at a first approximation the washout factors are the same in the two cases.

CONCLUSION

The foregoing has been a resume of some recent events and trends that have been changing the radioactive hazards met in some laboratory practices or changing our realization of some of these hazards. I hope they will stimulate further efforts to reduce these hazards to negligible proportions.

PREVENTIVE MEDICINE IN THE ATOMIC ENERGY INDUSTRY

D. W. S. Evans, *C. G. Stewart*, and *A. N. Marko*

For the purpose at hand we limit ourselves to consideration of the prevention of injury to employees by exposure to ionizing radiation and show, by the example of Atomic Energy of Canada Limited, how this matter is dealt with in Canada.

In the atomic energy industry as a whole, there exists the greatest range in the kinds and strengths of sources of ionizing radiation in use in any segment of society; consequently, a rather large and complicated organization is required to insure that employees are not injured by excessive exposure to ionizing radiation. "Excessive" in Canada means that we must not permit exposure of the employees such that the radiation dose received exceeds the limits that are implicit in the regulations under the Atomic Energy Control Act. When instructions in these regulations are not specific to particular real situations, we make use of the Recommendations of the International Commission on Radiological Protection. Because of the diversity in kind and magnitude of the radiation hazards in the atomic energy industry, it is obvious that the Health and Safety Organization—large and complex though it is—must have the extensive and continuous backing of various auxiliary services to provide on occasion specific technical assistance, advice, and instrumentation required.

The complexity and size of the whole organization is illustrated in figure 1.

The responsibility for health and safety within the Chalk River Nuclear Laboratories is shared between the Radiation and Industrial Safety Branch of the General Services Division, the Biology and Health Physics Division, and the Medical Division.

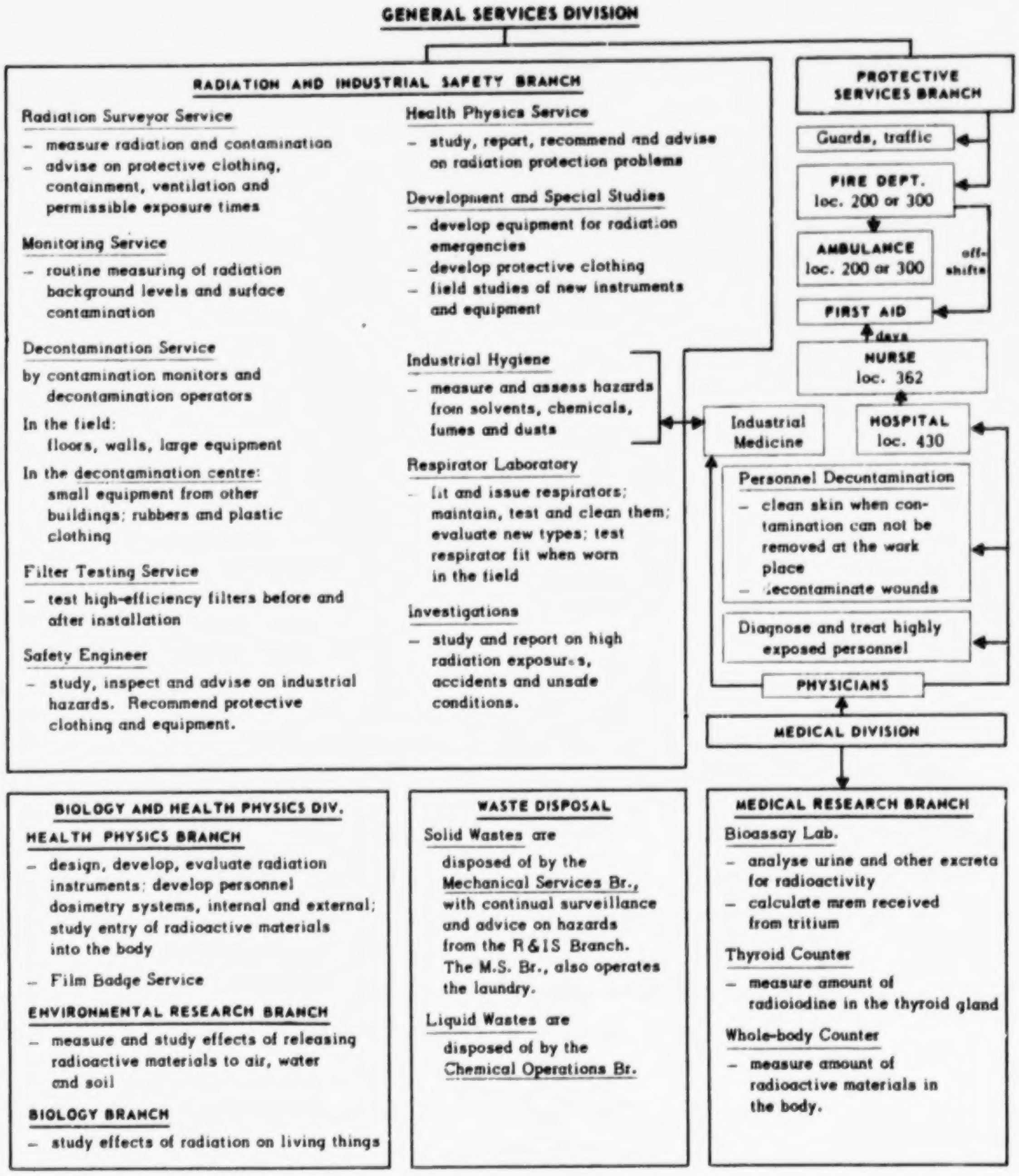

GENERAL SERVICES DIVISION
RADIATION AND INDUSTRIAL SAFETY BRANCH
Radiation Surveyor Service
– measure radiation and contamination
– advise on protective clothing, containment, ventilation and permissible exposure times
Monitoring Service
– routine measuring of radiation background levels and surface contamination
Decontamination Service
by contamination monitors and decontamination operators
In the field: floors, walls, large equipment
In the decontamination centre: small equipment from other buildings; rubbers and plastic clothing
Filter Testing Service
– test high-efficiency filters before and after installation
Safety Engineer
– study, inspect and advise on industrial hazards. Recommend protective clothing and equipment.
Health Physics Service
– study, report, recommend and advise on radiation protection problems
Development and Special Studies
– develop equipment for radiation emergencies
– develop protective clothing
– field studies of new instruments and equipment
Industrial Hygiene
– measure and assess hazards from solvents, chemicals, fumes and dusts
Respirator Laboratory
– fit and issue respirators; maintain, test and clean them; evaluate new types; test respirator fit when worn in the field
Investigations
– study and report on high radiation exposures, accidents and unsafe conditions.
PROTECTIVE SERVICES BRANCH
Guards, traffic
FIRE DEPT. loc. 200 or 300
AMBULANCE loc. 200 or 300
off-shifts
FIRST AID
days
NURSE loc. 362
Industrial Medicine
HOSPITAL loc. 430
Personnel Decontamination
– clean skin when contamination can not be removed at the work place
– decontaminate wounds
Diagnose and treat highly exposed personnel
PHYSICIANS
MEDICAL DIVISION
BIOLOGY AND HEALTH PHYSICS DIV.
HEALTH PHYSICS BRANCH
– design, develop, evaluate radiation instruments; develop personnel dosimetry systems, internal and external; study entry of radioactive materials into the body
– Film Badge Service
ENVIRONMENTAL RESEARCH BRANCH
– measure and study effects of releasing radioactive materials to air, water and soil
BIOLOGY BRANCH
– study effects of radiation on living things
WASTE DISPOSAL
Solid Wastes are disposed of by the Mechanical Services Br., with continual surveillance and advice on hazards from the R&IS Branch. The M.S. Br., also operates the laundry.
Liquid Wastes are disposed of by the Chemical Operations Br.
MEDICAL RESEARCH BRANCH
Bioassay Lab.
– analyse urine and other excreta for radioactivity
– calculate mrem received from tritium
Thyroid Counter
– measure amount of radioiodine in the thyroid gland
Whole-body Counter
– measure amount of radioactive materials in the body.

Figure 1. Distribution of Chalk River Nuclear Laboratories health and safety responsibilities.

The Radiation and Industrial Safety Branch advises all laboratory and operating groups on safe practices for working with radioactivity and in the vicinity of radiation fields. It is responsible for the routine monitoring and surveying of the working environment, and for the provision of various kinds of protective clothing and equipment. As its name implies, advice is also given on matters pertaining to conventional industrial safety.

The Biology and Health Physics Division is directly concerned, through its Health Physics Branch with the design and development of new instruments for the detection and measurement of radiation, the development and evaluation of personnel dosimetry systems, the provision of the personnel dosimetry services, and studies of the potential modes and rates of entry of radioactive materials into the body. Another important function of this division is the study and control of the spread of radioactivity into the environment.

There are two branches of the Medical Division concerned with radiation protection. The Plant Hospital is essentially an industrial out-patients clinic, and separate facilities have been added for the treatment of personnel who have been contaminated—or have sustained contaminated wounds. The Medical Research Branch is primarily concerned with the toxicology of radioactive materials; consequently, it is engaged in the assessment of the degree of internal contamination, evaluation of the dose to be received from internally deposited radionuclides, and with the principles of control of this particular hazard.

Education plays a major part in the protection of employees at Chalk River. All classes of new employees, who are expected to work occasionally or continuously in locations where radiation fields or radioactive elements could be encountered, attend a short course of instruction when they first join the company. This course embraces the nature of radioactivity and its biological effects, practical measures for avoiding internal and external exposure, the demonstration of safe techniques for the handling of radioactive materials, and other relevant subject matter. Subsequently, safety meetings are held at regular intervals for various groups of employees, at which further instruction is given in the principles of the control of radiation hazards, often by example. The educational process in our employ is a continuing one. As well, more extensive and detailed instruction is given to new employees of the Radiation and Industrial Safety Branch, and on occasion to outside groups such as radiation safety officers from nongovernmental organizations or from the armed forces.

Control of the spread of radioactive contamination that is necessary to protect the health of the employee, and to protect sensitive measuring instruments, is grossly provided by a division of the laboratories into an "active" area for work with radioactive substances in excess of trace amounts, and an "inactive" area for other operations. Movement of materials and equipment between these areas is severely restricted by considerations of contamination control. Employees who work within the active area are responsible for monitoring themselves for all types of contamination to which they may have been exposed before leaving their particular buildings; in the event of an accident, however small, or just the desire for advice, members of the Radiation and Industrial Safety Branch are always available. This aspect of personal hygiene is particularly important since appreciable amounts of alpha- or beta-emitting contamination could otherwise pass active area exit monitors without being detected. These interarea gates are equipped with fixed gamma-sensitive monitors on each side of the gate, and fixed beta-sensitive monitors on the floor. Practical considerations (for example, the amount of gamma-emitting radionuclides commonly found on wristwatch dials) determine the sensitivity settings of these monitors. Low though these settings may be, it is possible to pass these monitors without alarm and still carry an amount of surface contamination we deem undesirable from the point of view of contamination control. As well, at the interarea gates there is a plethora of special hand-operated monitoring instruments to be used in the assessment of the kind and degree of contamination in the event of an alarm.

Within the active area many of the buildings are similarly divided into "active" and "inactive" areas. Depending on the contamination potential in different buildings, a variety of control measures are afforded, from the provision of rubber overshoes and laboratory coats to respirators and complete changes of clothing, with facilities for showering and personnel decontamination. In areas where contamination levels may be high (for example, during maintenance operations on active systems), it is usual for decontamination personnel to assist employees with the removal of their protective clothing, and to search the skin and hair for contamination. Respirators worn under these circumstances are of course kept on until all contaminated clothing is removed, and until the employee is ready to leave the area of high contamination. A degree of contamination control is also effected by the filtration of effluent air from ventilating systems, and by the exhaustion of active air containing short-lived radionuclides through high stacks, to insure adequate dilution and time for decay before this air effectively reaches ground level. Within the active area, radiation surveyors and monitors search constantly for surface contamination by measuring radiation fields, by taking "swipe" tests to detect the presence of "loose" contamination, and keeping residual contamination levels as low as practicable. In the interests of economy, a decontamination center is maintained in which pieces of apparatus, tools, protective clothing, and equipment are routinely decontaminated, permitting their safe reuse.

In considering the control of internal contamination, it may be recalled that radioactive materials can enter the body by inhalation, ingestion, or by absorption through the intact or damaged skin. Control of the latter two routes of entry is provided first of all by education into safe working practices, such as the wearing of protective clothing, gloves, and by the use of remote handling apparatus. Control of the inhalation hazard presents greater problems, but this mode of internal contamination is reduced to a minimum by special attention to air monitoring, to the removal of loose surface contamination in the working environment, by good ventilation, and where necessary by the wearing of respirators or fresh-air-supplied breathing hoods.

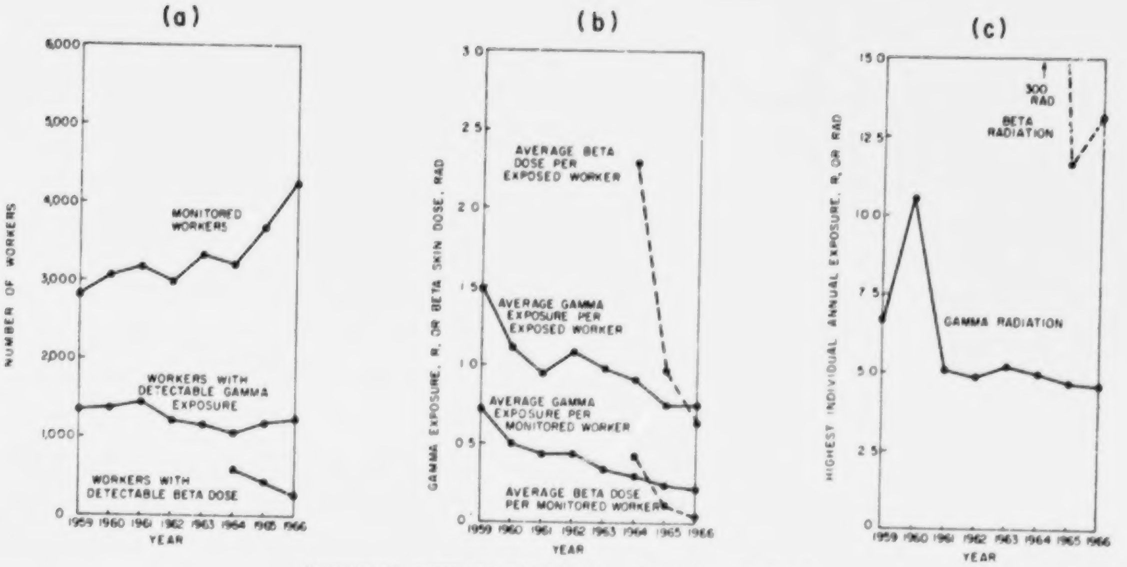
With regard to air monitoring, it is generally difficult to measure the concentration of airborne radioactivity both quickly and accurately. Apart from tritium, airborne radioactivity in our operations most commonly stems from fission products. In practice, respirators are worn on the advice of a radiation surveyor based on his experience, or when air monitoring indicates 100,000 disintegrations/min/m^3 of short-lived beta radioactivity or 1,000 disintegrations/min/m^3 of long-lived beta radioactivity. The short-lived radioactivity measured on air filters is mainly due to the ruthenium 88 daughter of krypton 88; it has an 18-minute half-life and implies airborne noble gas fission products. If air samples do not show clearly this half-life, or if this apparent half-life increases with time of decay, a much more hazardous mixture of fission products is assumed to be present. If relatively fresh (from the reactor) fission products are suspected, air is filtered through filters containing activated carbon. These filters are examined in a gamma-ray spectrometer for the characteristic photopeaks of the iodine fission products. Inasmuch as these are particularly toxic entities, demonstration of their presence in air makes the use of respirators mandatory. Finally, if fission product iodines are not present, and there is longer-lived beta-gamma radioactivity in the air other than that owing to noble gas fission products, the lower control limit of 1,000 disintegrations/min/m^3 becomes operative.

The presence of a toxicologically significant amount of long-lived alpha radioactivity in the air may be completely masked on occasion by relatively high concentrations of the alpha-emitting daughters of radon. For practical purposes, this difficulty is overcome by using an annular impactor with the air sampler. This apparatus collects dust particles with a diameter greater than about 0.5 micron. Since about 90 percent of radon daughters are attached to particles smaller than this, sufficient separation is achieved quickly to permit a meaningful estimate to be made of the alpha radioactivity in the air because of plutonium or uranium, for example. This method is used for "spot" or instantaneous air sampling. For continuous monitoring, advantage is taken of the apparent short half-life of radon products (circa 30 to 40 minutes) to permit distinction between these and longer-lived alpha emitters.

Internal contamination with tritium oxide is a practical problem at Chalk River because the Canadian atomic energy program makes large use of heavy water reactors. The greatest quantity of heavy water containing the highest concentration of tritium oxide is of course associated with NRU, the largest and most powerful reactor on site. Any operation (maintenance or experimental) that exposes even briefly the heavy water system to the atmosphere leads to airborne tritium oxide. A common point of release, for example, is at the top of the reactor, where a small amount of heavy water is exposed to the air during every fuel rod change. Tritium, as the oxide, can enter the body by inhalation and by direct absorption through the unprotected skin, at very nearly comparable rates. Practical control of this hazard is effected by education with respect to the special properties of tritium oxide, by the use of routine precautionary measures—including good housekeeping practices—adequate instantaneous monitoring of the working environment, exhaust ventilation—including flexible ducts which can be brought to the point of release—protective clothing, and fresh air hoods and masks.

The efficacy of all these protective procedures is measured finally by the records of film dosimeters, and of a variety of other personal dosimeters used on special occasions for special purposes. Thermoluminescent dosimetry, for example, is playing an increasing part in the measurement and control of beta doses to the skin. Internal contamination is signaled by the reports of the Bioassay Laboratory on the basis of routine and "spot" special urine analyses carried out for specific radionuclides to which exposure is suspected to have occurred. Figure 2 summarizes the radiation exposure records of the monitored workers over the past 8 years.

The number of employees with detectable gamma exposures has remained fairly constant despite a considerable increase in the number of monitored employees. Since 1964 (the first year in which adequate beta dosimetric procedures became available to us) the number of employees with detectable beta exposure has declined steadily. This decrease in the average beta-ray dose is attributable to a considerable extent to an active and continuing educational program. In 1966 the highest individual exposures from external beta and gamma radia-



(ASSESSMENT OF BETA RADIATION DOSE WAS NOT MADE PRIOR TO 1964)

Figure 2. Summary of results over an 8-year period.

tion were below the limits set in the regulations under the Atomic Energy Control Act. Most of the beta doses at Chalk River are received during the preparation of radioactive sources, during the examination of irradiated materials, and in the decontamination and repair of contaminated equipment—operations in which the hands are brought into fairly close proximity to the source of radiation. The use of thermoluminescent dosimetry now permits a much better assessment of the skin doses, and experience so far has shown that these doses are not trivial.

Figure 3 shows that the control of the tritium oxide hazard in 1966 was less satisfactory than desirable for reasons which are not entirely clear; the average dose was about 50 percent higher than in the previous 2 years.

Although the maximum doses received were still well within the maximum doses permissible, it is an unsatisfactory state of affairs and one that we are attempting to remedy. It is perhaps relevant that the highest single dose from a tritium oxide exposure ever recorded at Chalk River is about 3 rem. In the current year tritium exposures are (so far) once more at lower levels, and it is clear therefore that the rise in 1966 cannot be attributed alone to the increasing concentration of tritium oxide in the heavy water with reactor operating time.

It is also clear that in spite of careful control, it is possible for occupationally exposed workers to receive a total radiation dose in

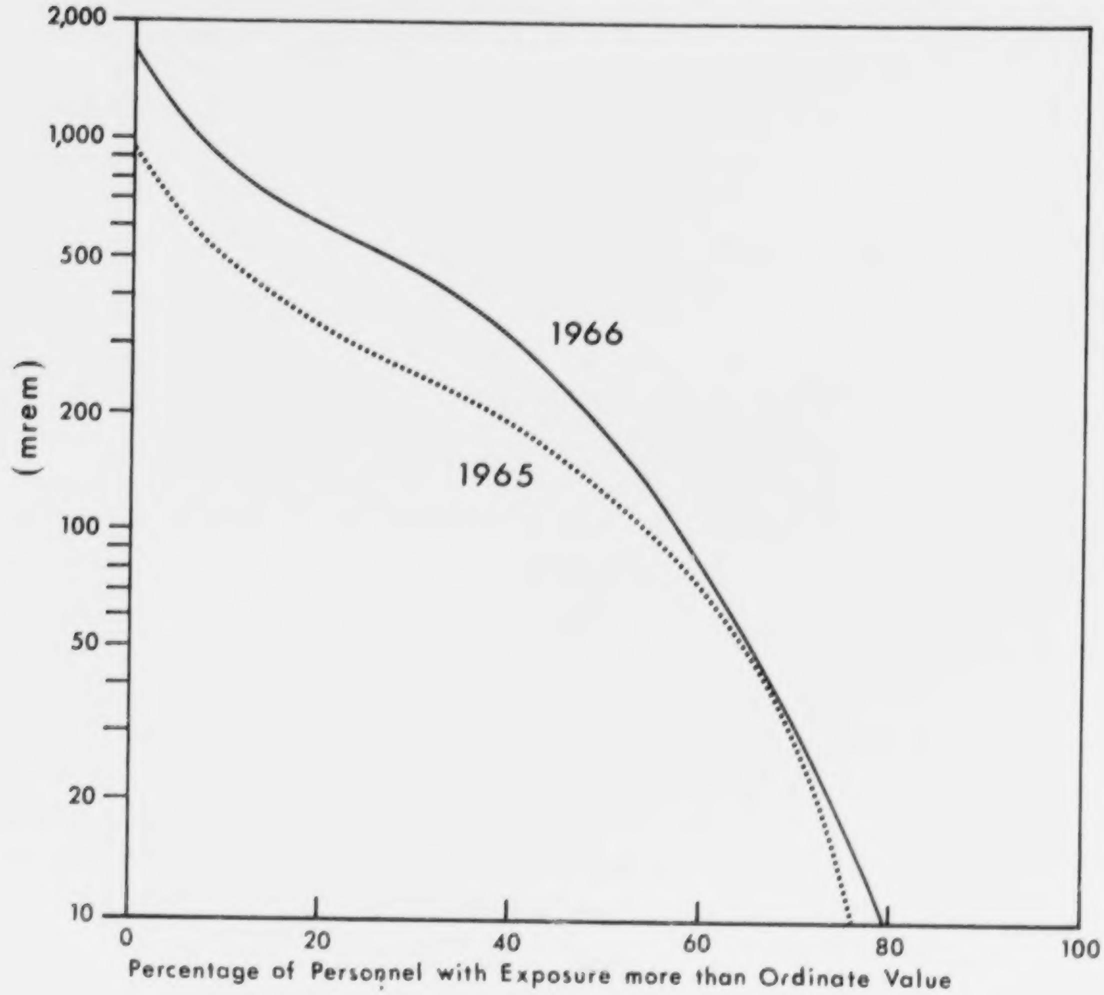


Figure 3. Distribution of tritium exposure in tested Chalk River Nuclear Laboratories personnel.

excess of the permissible annual maximum, and one such case occurred in 1966 (fig. 4).

Another important aspect of preventive medicine in the atomic energy industry is the measurement and control of the radiation hazard attending the mining and processing of uranium ore. It has been known for many years that miners employed during the last century in the Joachimsthal and Schneeberg mines suffered a high incidence of carcinoma of the lung. The ore body in these mines contains uranium, and the mine air contains radon 222 and its short-lived daughters. On the basis of recent studies in Newfoundland (*1*) and in the Colorado Plateau (*2*), the suspicion that radon daughters are the primary cause of the observed incidence of lung carcinoma has become a virtual certainty.

Measurement of airborne radon and daughters in various mines in Canada began in 1952 using equipment designed and built at Chalk

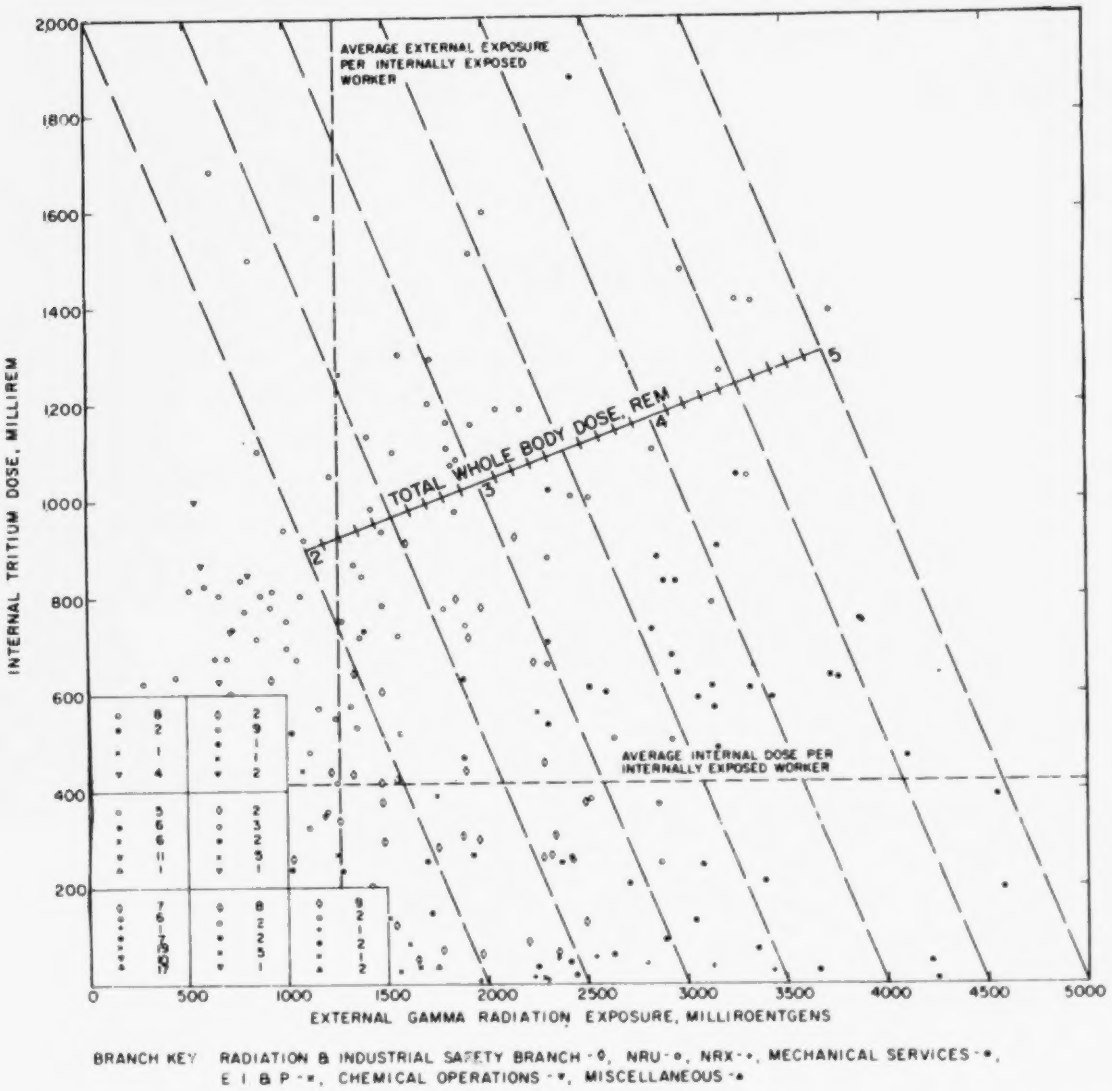


Figure 4. Distribution of external and internal doses by branch (includes only those workers with internal tritium dose). No terminations.

River. These early investigations and those subsequently carried out in 1954 indicated a need for supplementary and controlled ventilation of the mines. By 1956, the median concentration of airborne radon daughters in the atmospheres of the major groups of mines had been reduced to the then maximum permissible ICRP level of 10^{-10} curies/liter (*3*, *4*). The ICRP amended this level in 1959 on the basis of new evidence available to it, resulting practically in a threefold reduction of its 1955 maximum permissible level. Continuous and strenuous efforts are being made by the uranium mining companies in Canada to attain this recommended standard in various areas in the mines.

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RADIOACTIVITY HAZARDS IN EXPLOITATION OF NATURAL RESOURCES

Victor E. Archer

Out of more than 50 naturally occurring radionuclides, the only ones that have been demonstrated to injure the health of workers without artificial enrichment are radon 222 and its immediate daughter products. Radon, a noble gas, diffuses out of host rock, is dissolved in water, and collects in cavities, such as mine workings. Its short half-life daughters (isotopes of polonium, lead, and bismuth) become in great part attached to dust particles in the air and are inhaled by miners, and they are filtered out of the air in the lungs. This results in potentially large radiation doses from alpha particles to bronchial epithelium. A similar situation exists with radon 220 (thoron) and its daughters, but no human injuries have been observed from them because underground thorium ores have not been exploited, and thoron hazards are more easily controlled by ventilation. Radon and its daughters may occasionally be found in considerable amounts in ground water. Dissolved radon escapes so rapidly when water is exposed to air that injuries from ingestion have not been observed. Occasionally radium is sufficiently concentrated in rich ores or plated out from water running through metal pipes, and an external hazard from gamma rays may be present; however, no injuries from such exposure have been demonstrated.

Excessive rates of lung cancer have been found among underground miners exposed to substantial amounts of radon and its daughters in silver-copper-uranium ores of Schneeberg, Germany, in silver-nickel-uranium ores of Joachimsthal, Czechoslovakia, and in fluorspar mines of Newfoundland. Extensive studies of uranium miners working in the Colorado Plateau area of the United States have confirmed and extended the older findings of injury. These miners were examined periodically between 1950 and 1960. Epidemiological analysis of these medical findings in conjunction with environmental surveys disclosed a number of findings and interesting associations. One of the things we have done in medical examinations is to collect sputum samples from uranium miners. Sputum samples have been collected most of the time with the aid of an aerosol which helps the person to cough and produce some sputum. The sample is then concentrated, put on slides and stained by the Papanicolaou technique. Figure 1 is a set of three sputum curves from the same group of sputum samples obtained from 1956 to 1963. Class IIIA and Class III sputum means that some cells were found that carried some suspicion of cancer. When the percent of samples read as suspicious are distributed on the basis of age, the line runs nearly straight across the graph. This means that there was no association between age as such and the percentage of men having suspicious sputum. The solid line is a distribution curve based on total cigarettes used. The three points represent nonsmokers plus light smokers, moderate, and heavy smokers. This line is nearly straight across the graph also, although it does have a tendency to rise. This rise is not statistically significant. This means that there is very little association between cigarette smoking and the percentage of men with suspicious sputum. The dashed line represents the distribution curve based on years of underground uranium mining experience. The men who had very little experience had practically no suspicious samples, whereas with increasing years of uranium mining experience there is a definite increase of the percent of men who have suspicious sputum.

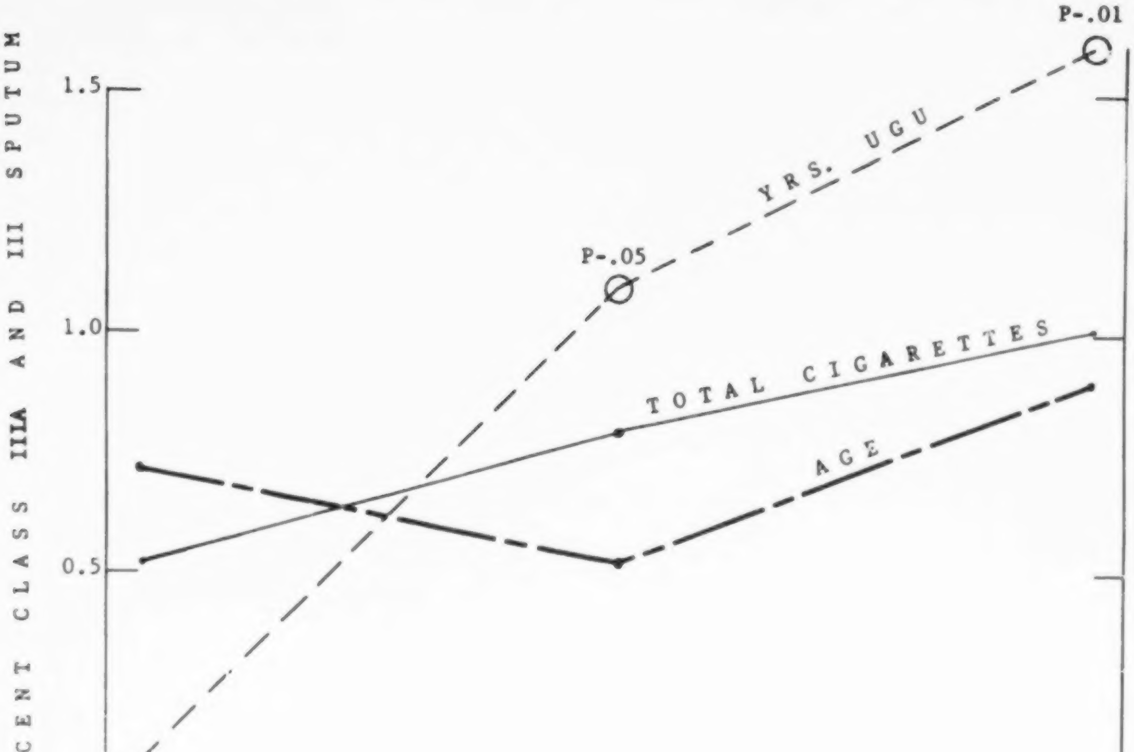

Figure 1. Association of age, years underground uranium experience, and smoking with Class IIIA and Class III sputum.

Figure 2 shows the analysis of one symptom of chest disease. The symptom is persistent or chronic cough and represents the results from 2 different years of examination. The first portion of figure 2 represents the rather simple analysis for 1957 in which the men were divided on the basis of their mining experience. The three groups were adjusted for age, and smoking habits were not considered in this particular analysis. The slope of the curve indicates rather clearly the association between persistent cough and years underground in uranium mines. In 1960, we did a more sophisticated analysis. The men were divided into several different groups, on the basis of age, cigarette smoking, and "R.I." or Radiation Index. Radiation Index is a rough measure of cumulative radiation exposure. The fact that the age curves (in the remaining portion of fig. 2) are separated means that there is an increased association between age and persistent cough. The fact that the two curves for heavy smokers are located higher than the corresponding curves for light smokers indicates that there is an association between persistent cough and smoking. The slope of the curves are dependent upon cumulative radiation exposures. Here we show a very sloping curve with a very sharp association between cumulative radiation exposure and a fraction of the men having persistent cough.

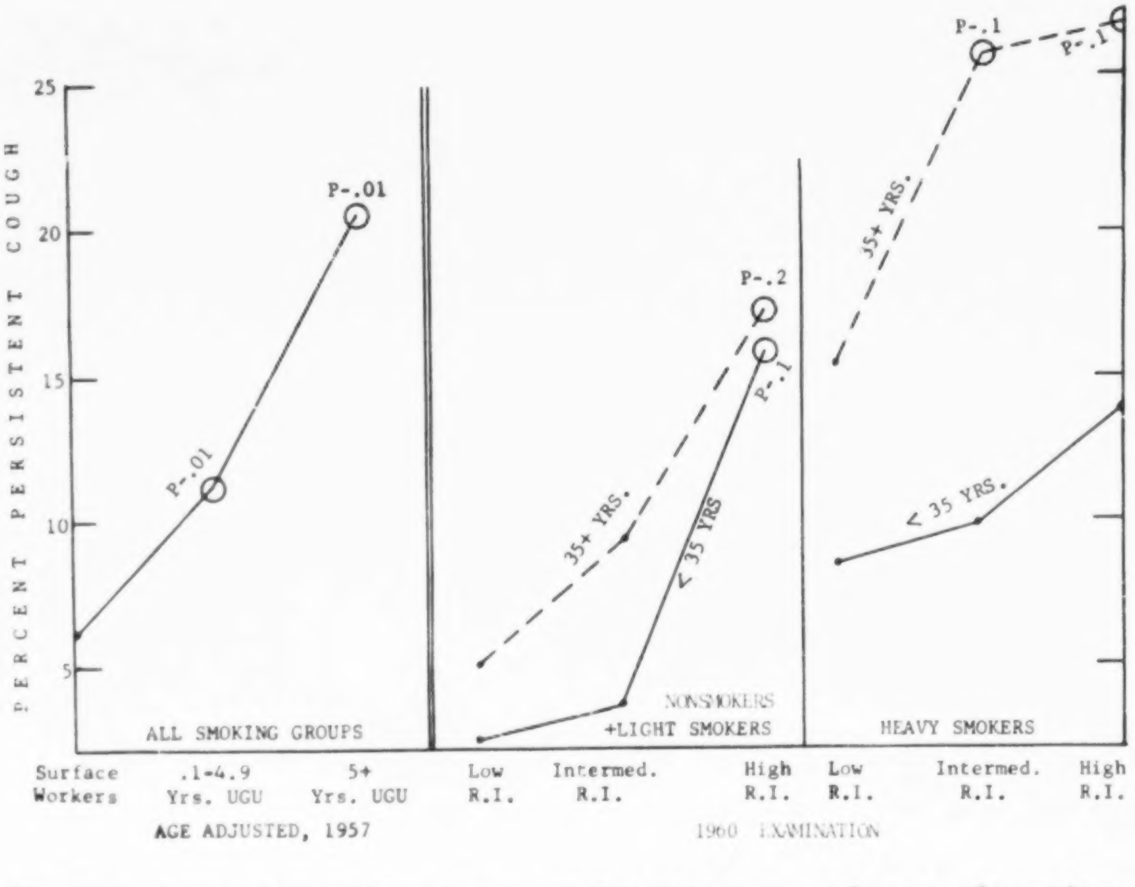

Figure 2. Association of "persistent cough" with years underground uranium experience, Radiation Index, age, and smoking.

Curves for other symptoms of chest disease, such as wheezing, chest pain, and shortness of breath, are very similar to those in figure 2, which shows the same associations.

We also checked for associations with a number of findings that were found or observed by physicians. Figure 3 deals with "impression of emphysema" obtained by the physician. This impression was based on increased anterior-posterior diameter of the chest, distant heart sounds, and so forth. Just as with "persistent cough," there is an association between the fraction of men giving an impression of emphysema and age, cigarette smoking, and Radiation Index.

We have similar curves for ventilating function tests. They show essentially loss of ventilatory function associated with increasing age, increasing cigarette smoking, and increasing Radiation Index.

In 1957, we examined hair roots for abnormalities. With forceps, we plucked 30 to 50 hairs from the head of each miner, put the hair roots into a dilute formalin solution and later examined them under a low-power stereoscopic microscope. Figure 4 is a preliminary analysis done on them. It shows almost 30 percent abnormal hair roots in the underground uranium miners—about twice as many as found among coal miners. The total percentages of deformed roots may have

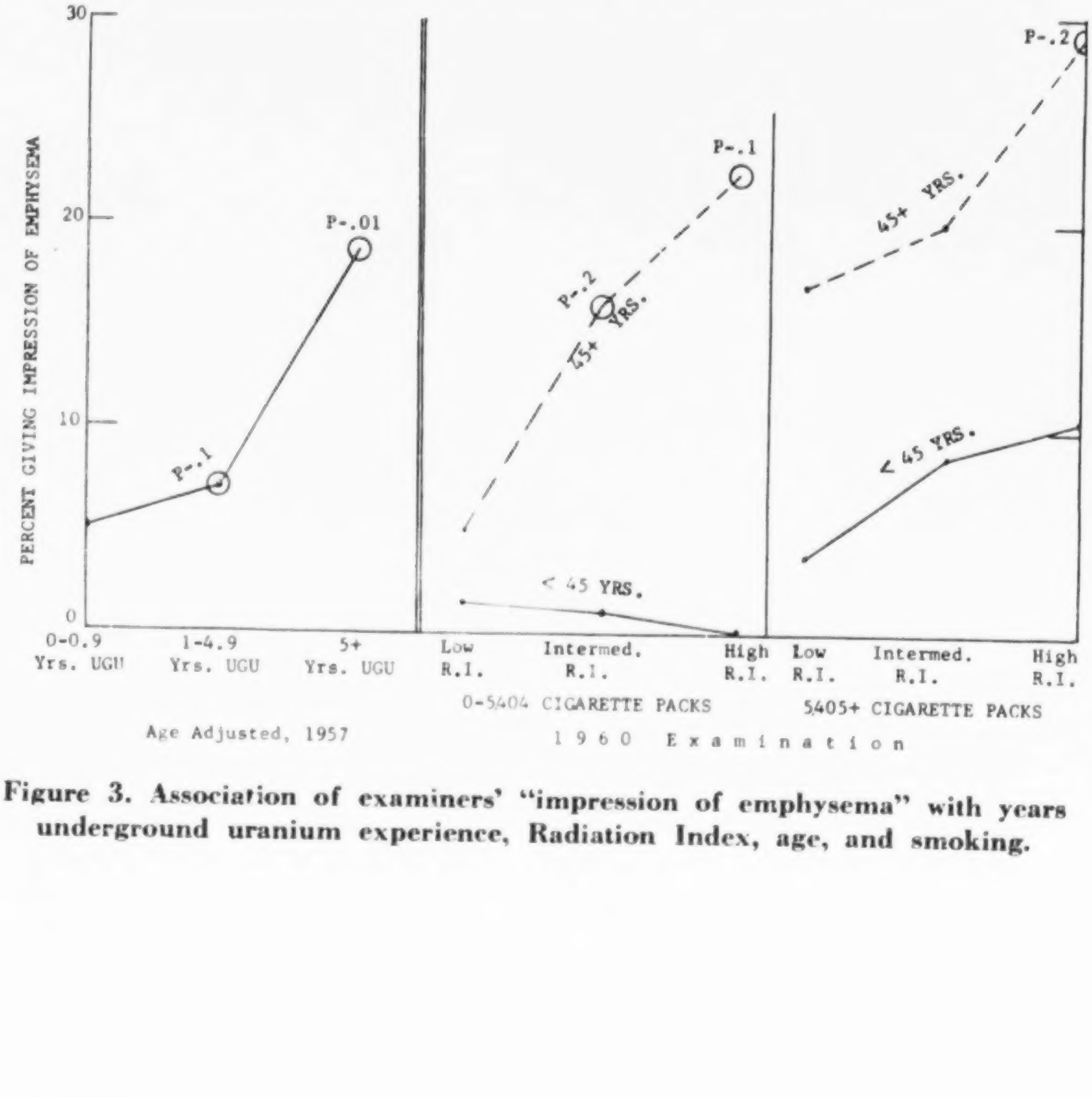

Figure 3. Association of examiners' "impression of emphysema" with years underground uranium experience, Radiation Index, age, and smoking.

been somewhat artificially elevated by our technique, but the same technique was used for both groups so the results are fully comparable. Men who had very limited uranium mining experience, or had quit mining, had rates of hair root abnormalities intermediate between coal and uranium miners.

Periodic followups of the uranium miners examined have given information on disability and death. There are excess deaths among the uranium miners studied from lung cancer, work-related accidents, and from pulmonary fibrosis. Some of this fibrosis may be the results of silicosis, but we feel that part of it has been due to a radiation effect.

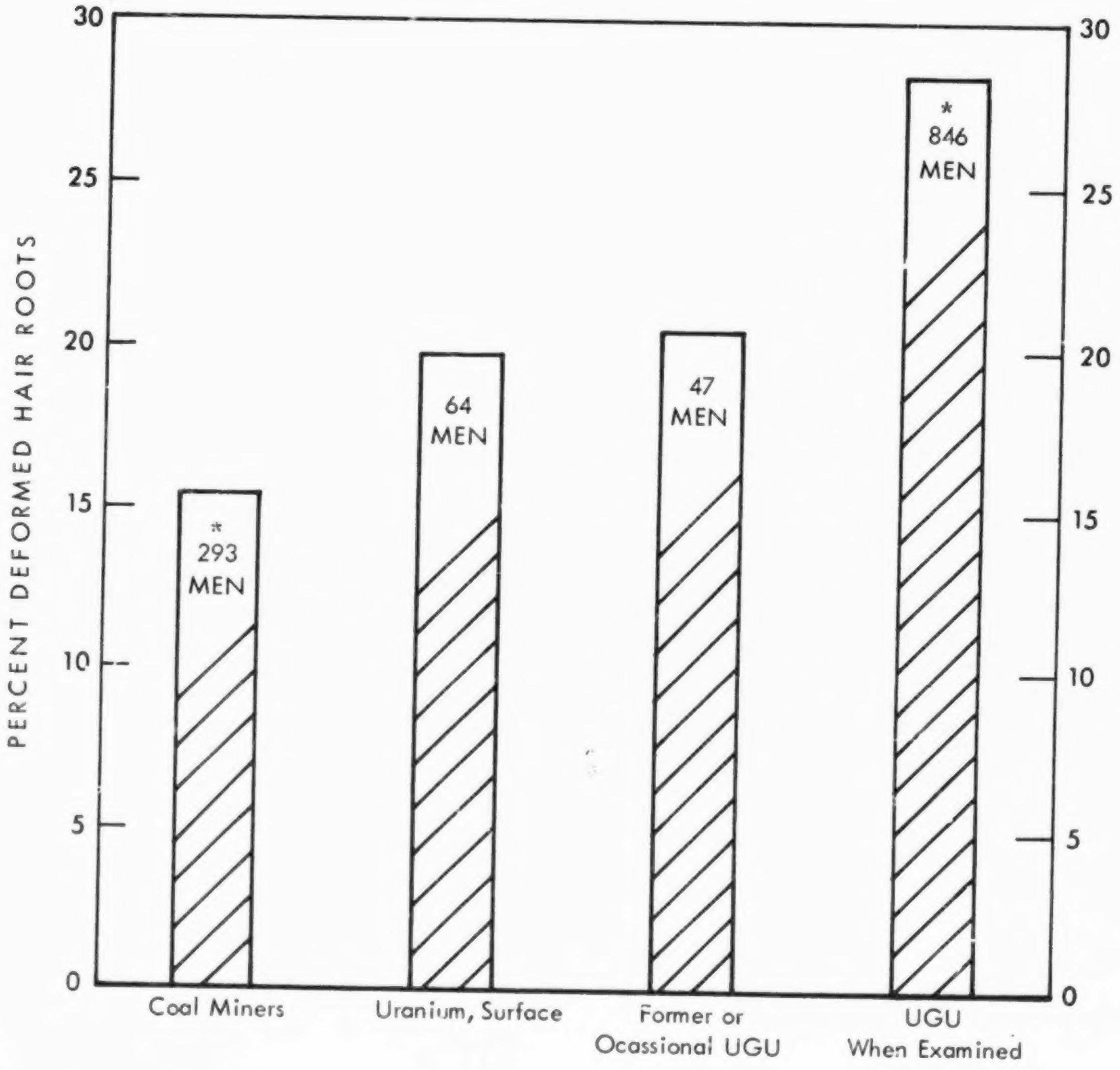

Figure 4. Prevalence of deformed hair roots as associated with type of mining activity. Asterisk indicates significant difference (P<.01) from either center groups.

The most recent mortality analysis was done on 3,413 white men who had worked underground. The men were divided into groups on the basis of cumulative exposure to radiation as shown in table 1.

In the first column, cumulative exposure is expressed as working level months (WLM); that is, the average working level in a mine for each year was multiplied by the number of months each man spent in the mine, and added for successive years. The second column gives man-years, rather than individuals for two reasons: some of the men were followed for longer periods of time than others, and individual men were moved from one exposure category to the next as their cumulative exposure increased. The third column gives the number of certified lung cancers observed in each group. The fourth column gives the calculated "expected" number of lung cancers. These numbers were calculated on the basis of lung cancer rates in the States where the men were working, the man-years in the group and the age distribution of the individuals contributing the man-years. The fifth column expresses the observed lung cancers among the uranium mining groups as incidence. The last column makes it quite clear that the lung cancer rate increases rather sharply as cumulative exposure is increased.

In addition to the 37 lung cancers indicated in table 1, there are 30 more probable lung cancers among the study group. They were not included in the table either because they appeared after the last day included in the analysis or their death wasn't clearly ascrible to lung cancer because of the way the death certificate was written.

This study group is only a portion of the uranium miners working in the Colorado Plateau. If we count all the other lung cancers that we know about, and add these six, there are presently over 100 lung cancers among U.S. uranium miners.

Table 1. ***Certified respiratory cancer deaths among underground U.S. uranium miners, 1950–65***

Cumulative exposure (WLM)	Person-years	Observed lung cancers	Expected lung cancers	Observed cases per 10,000
<120	8,783	2	1.90	2.28
120 to 359	7,588	7	1.73	9.23
360 to 839	5,793	4	1.60	6.90
840 to 1,799	3,949	8	1.17	20.26
1,800 to 3,719	1,921	9	.68	46.85
≥3,720	545	7	.18	128.44

As we began to see increasing numbers of lung cancers among uranium miners, we began to notice that they were acting a little differently than lung cancers seen among other people. The cell types described in the Schneeberg and Joachimsthal areas seem to be predominately small-cell undifferentiated types, and were sometimes mistaken for sarcomas. To check this, we did an analysis using 51 uranium miners with lung cancers for whom we were able to determine the cell type of the cancer, and compared them with 51 lung cancers among nonminers, matched on the basis of age and cigarette smoking habit. We had trouble matching some of the uranium miners, because the lung cancers did not seem to appear among the general population at as young an age as it did among uranium miners. The results are given in figure 5. The first two columns, with uranium miners versus the matched controls, show that the epidermoid-cell types were much more frequent among the nonminers and that an increased proportion of small-cell undifferentiated types were mainly responsible for the difference. In further analysis, the uranium miners were divided into three groups on the basis of cumulative exposure to radiation. The cell type distributions were again compared. A striking difference was observed between these three groups. The percentage of small-cell undifferentiated tumors increased with increasing exposure, and a de-

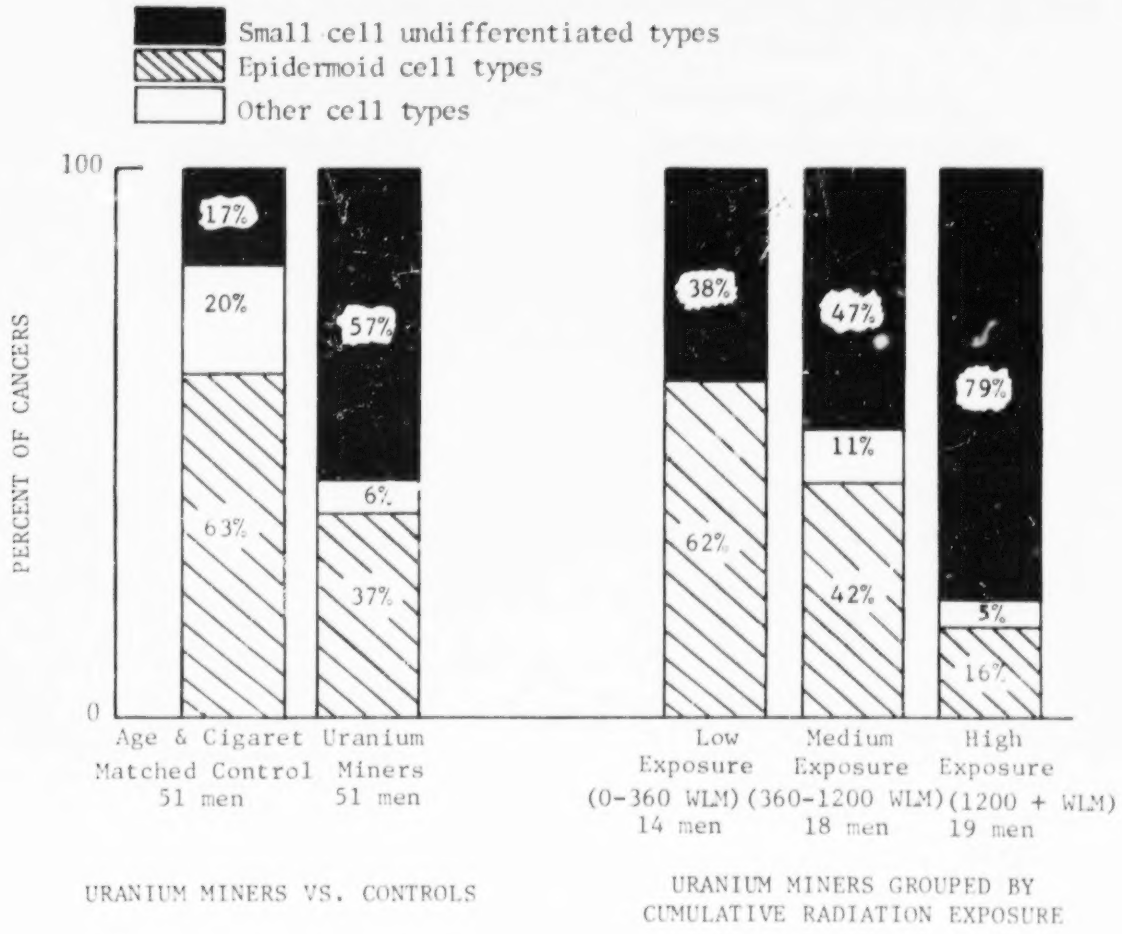

Figure 5. Relative percent of different cell types of lung cancer among uranium miners and controls.

crease in the number of epidermoid cancers was found. This type of analysis does not tell us whether or not epidermoid cancers were also increased among uranium miners; certainly it provides good evidence that the small-cell undifferentiated is. Some of our later data seems to indicate that both these main types are increased but that the small-cell undifferentiated is increased to a much greater extent than the epidermoid ones. Adenocarcinomas are quite rare among uranium miners.

Urine and tissue samples from some uranium miners have been analyzed for lead 210 and polonium 210. Figure 6 gives data from six cases in which urine samples were obtained before the men died. The ratio between the urine and the bone content of lead 210 is plotted. It shows the type of curve that one would expect, although it's a relatively small amount of data and each point represents a different man. It does show a fairly rapid excretion ratio early after the last of continuing exposures, and indicates at least two phases of excretion. The initial phase, no doubt, represents excretion from body fluids and soft tissue, whereas the second phase almost certainly represents excretion from bone deposits. This means that samples obtained during exposure or shortly after will largely reflect current or recent exposure, whereas urine samples obtained later (3 to 10 months, post exposure) will more fully reflect the cumulative exposure.

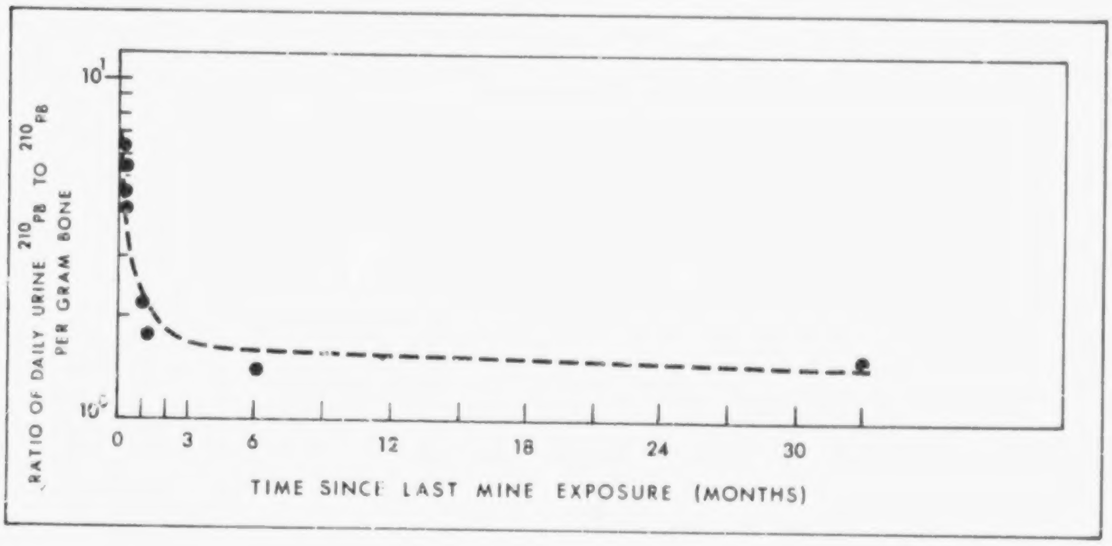

Figure 6. Ratio of lead 210 in urine versus lead 210 in bone compared to time of last mine exposure.

In figure 7 the concentration of lead 210 in the bone of uranium miners is plotted against cumulative exposure. Nearly all are autopsy data, with one exception, which is from an amputation. The working level months (WLM) is based partially on measurements in mines and partly on estimates, when there were gaps in the data. There is considerable scatter of the data, but there is also a very definite pattern. It was felt that adjustment for excretion might reduce the scatter.

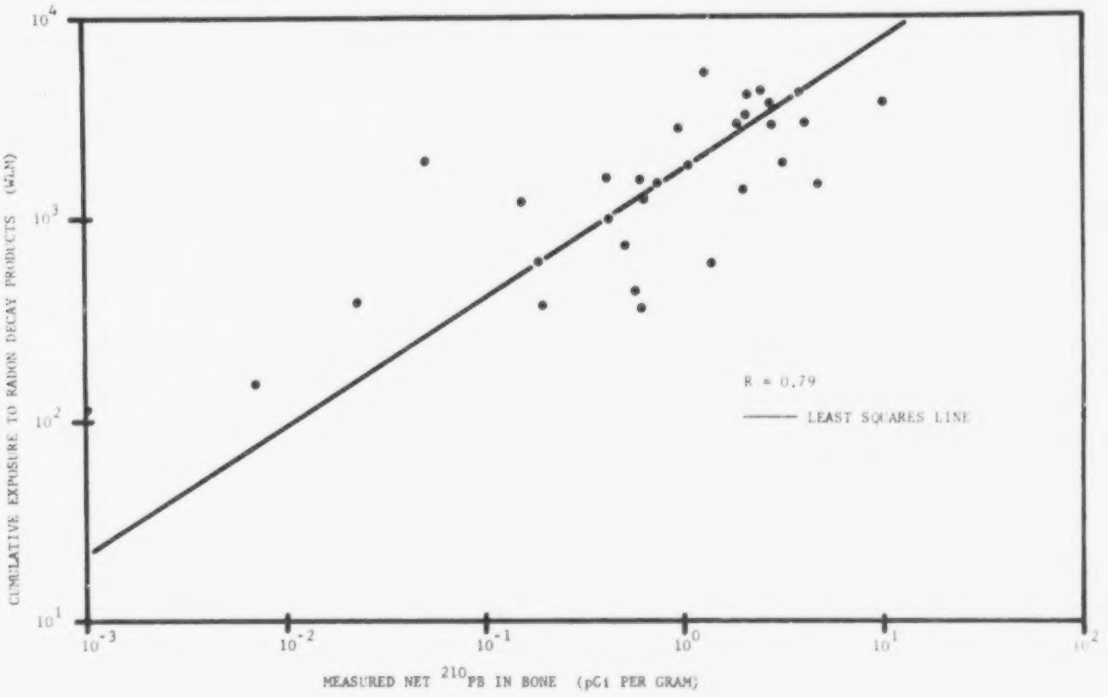

Figure 7. Concentration of lead 210 in bone versus cumulative exposure.

Figure 8 gives the results of those efforts, in which adjustment for excretion was made since the last exposure. This may be an oversimplified adjustment, but it does improve the correlations considerably. We have sought a similar association between working level months and the lead 210 in urine and in soft tissue. We have not found nearly as good a correlation as was seen with bone. I suspect that one of the reasons for this is that with the urine and soft tissue, we are dealing with two different aspects of exposure. One is the intensity of recent exposure, the other is the magnitude of cumulative exposure. Our information simply was not good enough to be able to separate the two aspects with the material we have had.

A number of attempts have been made to determine what is a safe level of radon daughter exposure. If there is no threshold for the production of injury by radon daughters (and most radiation safety concepts are based on the no threshold theory), then we must try to determine quantitatively, the risk of lung cancer at the lowest levels which are practical to obtain in uranium mines. I, personally, have seen no hint of a threshold in our data on uranium miners, although some people profess to see one. Figure 9 represents one of our efforts

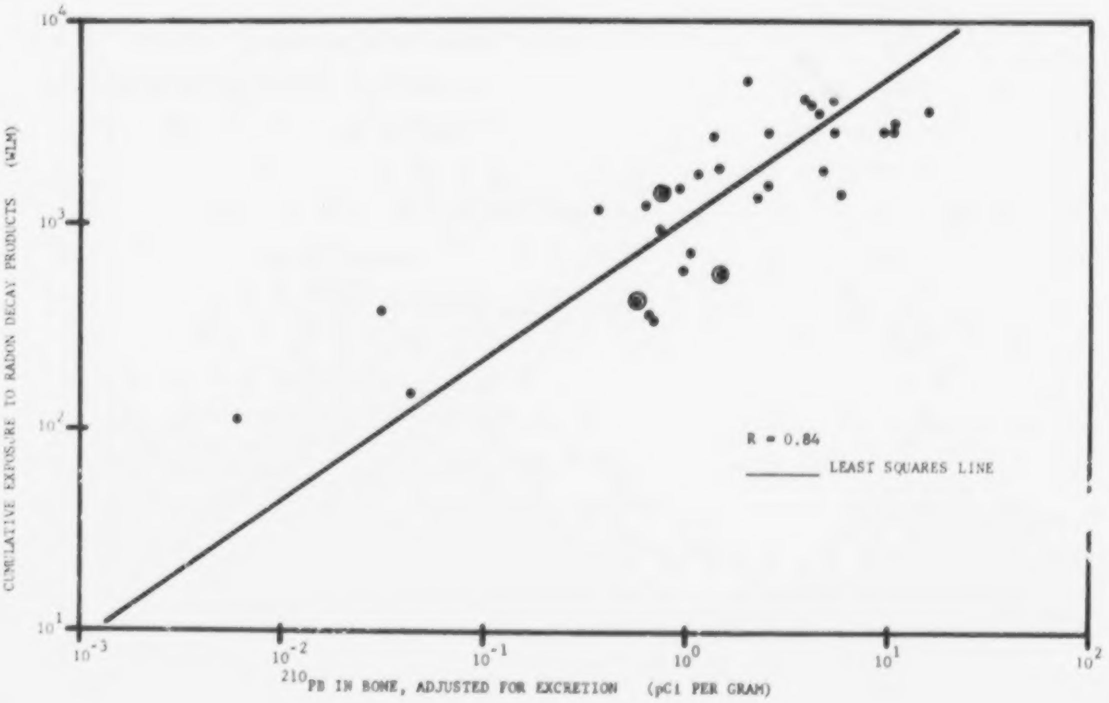

Figure 8. Concentration of lead 210 in bone versus cumulative exposure, adjusted for excretion.

to evaluate the risk at low levels. In this graph, I have taken whatever information I could get from the literature on the Joachimsthal, Schneeberg, fluorspar situations, data from our U.S. uranium miners, and data from a metal mining group. Whenever possible, the miners were divided into subgroups on the basis of mean exposure for that group. In figure 9 there are three graphs, which use three different methods of measuring lung cancer. Percent of deaths because of lung cancer is the crudest method. The second method is the observed divided by expected, which gives a ratio. The third method uses incidence. In plotting the points for some of the groups it has been necessary to make some estimates in order to fill in gaps in the data. The vertical and horizontal lines represent approximate 95-percent-confidence limits, being based on the numbers that we had and the lines being extended on the basis of how reliable the data was thought to be. It is surprising how these different data fit together, in spite of the fact that in order to put them together this way we have to make a number of assumptions about age distribution and other factors, assuming that they are not of much importance, and assuming that the overriding factor in lung cancer here was the exposure to radon daughters.

The sigmoid curve, based on the probitanalysis didn't really seem to fit very well. The quadratic regression curve and the visually fitted straight line are very similar and seem to fit the data much better than does the sigmoid curve. The straight line, therefore, appears to provide a good basis for computing radiation safety standards. At least it is a prudent position to take. From the slope of this line, it can be calculated that the doubling dose for lung cancer is approximately 120 working level months. This represents one man exposed at one working level for about 10 years. This is in substantial agreement with the estimate made recently by our Federal Radiation Council, which in looking at the data said that the doubling level was probably somewhere between 100 and 400 working level months.

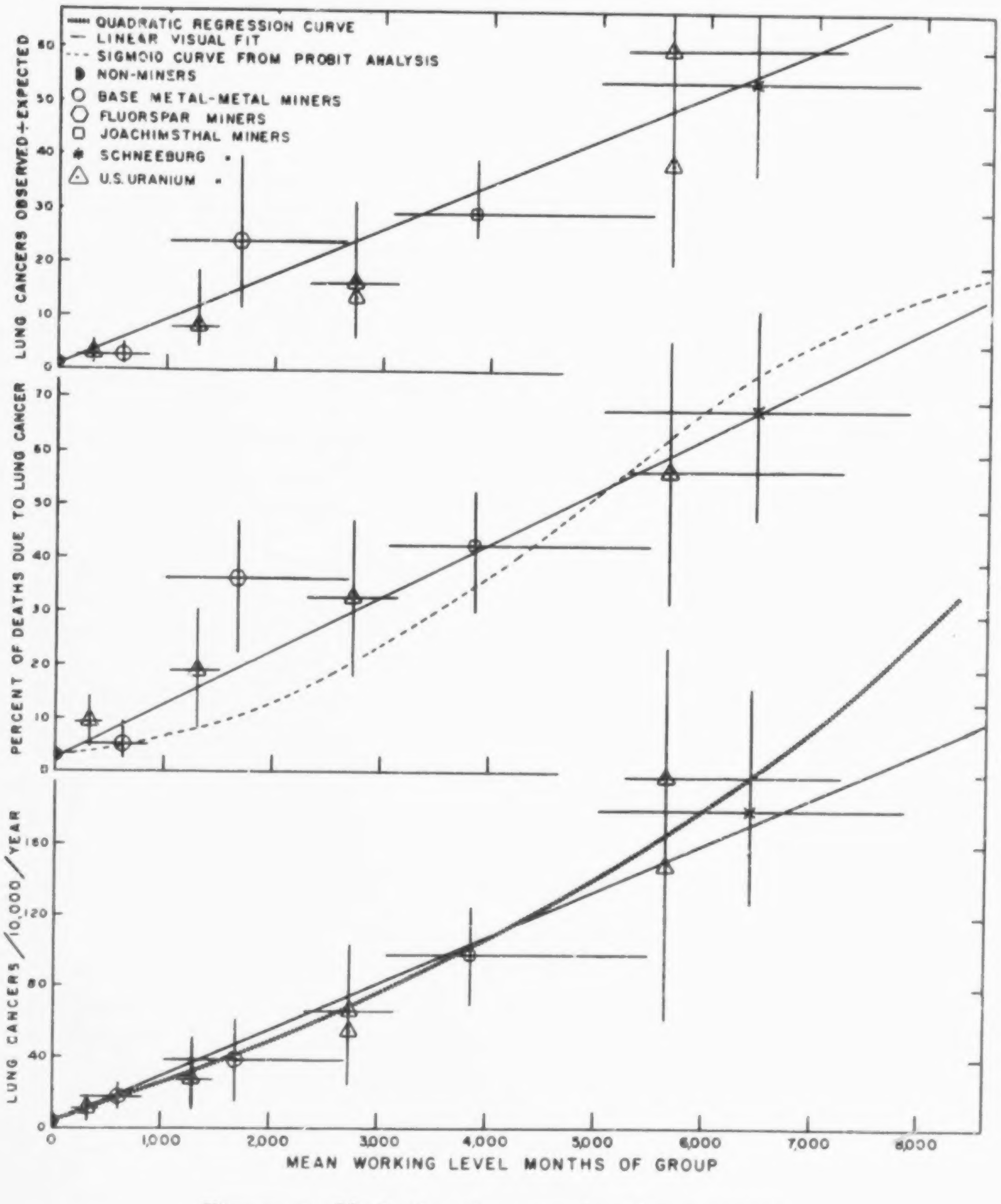

Figure 9. Methods of measuring lung cancer.

PREVENTIVE MEASURES IN EXPLOITATION OF NATURAL RESOURCES

Duncan A. Holaday

Uranium miners are exposed to all of the occupational hazards that are generally present in underground mining operations such as silica dust, toxic smokes, and gases from the use of explosives; diesel engine exhaust gases: excessive noise; and a variety of physical hazards. Additionally, uranium miners are exposed to external beta and gamma radiation from the ore bodies, and internal radiation from airborne radioactive elements which are inhaled and deposited in the respiratory tract.

Usually, the hazard from external radiation is minor compared with that from internal radiation, and the primary internal radiation hazard is created by exposure to radon 222 and its short-lived daughters.

An understanding of the physical and radioactive properties of radon and its daughters is necessary before it is possible to assess the problems involved in controlling contamination of working areas in mines by these elements and to design useful control procedures. Radon is a noble gas, about seven times as dense as air, with a half-life of 3.8 days. It is produced continuously by the decay of radium in the ore body and diffuses through the host rock into open areas in mines. The daughters of interest, RaA, RaB, RaC, and RaC′ (polonium 218, lead 214, bismuth 214, and polonium 214), are formed in the mine air by successive transformations. These elements have half-lives of 3.05 minutes, 26.8 minutes, 19.7 minutes, and 164×10^{-6} seconds, respectively. They are formed as individual, highly charged atoms which diffuse rapidly and attach themselves to the first surface encountered. As a result, essentially all of the airborne radon daughters are on submicron particles or exist as unattached atoms. All of these characteristics influence the design of control procedures.

Many individuals in uranium mines have studied methods for controlling atmospheric concentrations of radon and radon daughters in uranium and this discussion will undoubtedly overlook some excellent and significant work, however, it is difficult to keep up with progress in this field, and much work has not been reported. If proper acknowledgment is not given to some investigators, it will be because of oversight. Methods for controlling atmospheric concentrations of radon and radon daughters can be described under these general classifications; removal of the contaminants from the working area; preventing the release of radon into working areas, and personal protective measures. At least the first two procedures must be used to obtain effective control.

General dilution ventilation has been the primary method of control. As each uranium mine presents its own special problems, detailed operating rules cannot be given, but general suggestions can be made. The first and most important item is for the mine ventilation plan to be designed in conjunction with the ore extraction plan before exploitation of the ore body is started. This procedure will assist in selecting the best compromise between the requirements of the mine ventilation engineer and the production engineer, and will prevent many troublesome problems. Uranium mines will require more ventilation than is normally necessary for metal mines, a fact that has often been neglected in planning.

The prime objective in dilution ventilation for removing radon and radon daughters is to introduce uncontaminated air to the working areas in sufficient quantities to maintain the radon daughter concentrations below the recommended levels. This objective may be impossible to meet, either from a technical or economic aspect, but every effort should be made to approach this goal. Detailed discussions of planning ventilation and estimating ventilation requirements are given in the book, "Problems of Occupational Hygiene in Underground Uranium Mines" (in Russian) (*1*). Among other reports on this subject are those by Yourt (*2*), Smith (*3*), and Holaday et al. (*4*). Well-known principles of mine ventilation apply, except that much more attention must be given to preventing the air supply from becoming contaminated; insuring that air is not recirculated; maintaining the integrity of airdoors and stoppings; and other standard maintenance procedures.

Dilution ventilation not only removes radon, but by shifting the equilibrium ratios between radon and each of the succesive daughters, reduces the potential alpha energy content of the air more than would be anticipated. This process is described by Tsivoglou and Ayer (*5*) and in references (*1*) and (*4*). Procedures for estimating the quantities of ventilation air required are reported by Harris and Bales (*6*) and by Kusnetz (*7*).

It is possible to remove radon daughters from the air by filtration, and this procedure may be useful in limited areas, such as a single small stope; however, as there is no practical means of removing radon from air, the daughters will grow in, so air must be continuously recirculated through the filter. Experimental work on such supplemental methods of control has been reported by Coleman et al. (*8*) and also in reference (*4*).

Reducing, as much as possible, the influx of radon into the mine is an important part of a control program. The first part of this program is to limit the source which will emanate radon. If the ore body is sufficiently extensive and well defined, haulageways and air courses should be kept at a minimum, and the inactive areas sealed. Experience has shown that pressure rather than suction ventilation systems should be used, particularly for ventilating headings. Materials, such as polyurethane foams, are practically impervious to radon and can be used to seal areas or surfaces. The techniques of applying these materials is an art, rather than a science, and much of the work is not published; however, methods of constructing stoppings, which will retain their integrity, have been developed. It would, indeed, be costly to line air courses with expanded foams, but it is also very expensive to provide additional ventilation.

Personal protective equipment must be considered in any control program as there are limits to the quantities of ventilation air that can be introduced into working areas. Men cannot work in excessively high flows, and the linear velocities that are required in some cases resuspend dust from the surfaces of air courses and drifts; thus, it is possible to introduce a larger hazard from silicosis than the radiation hazard which the program is designed to control.

Respirators have always been considered to be the last recourse for protection of workers. Respirators that are effective against toxic doses usually have such high resistances that men cannot wear them for extended periods. Filter materials are available which are very effective in removing radon daughters and still have low resistances by usual respirator standards. It is highly probable that respirators will assume a more important phase in a control program as the limits of effectiveness of the other methods are reached.

Controlling radiation hazards in uranium mines is not an easy task, and will require utilization of several different procedures. The problems are well understood and a large amount of information is available in the literature. Constant attention must be given to this problem to insure a safe working environment.

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THE ROLE OF MARINE PLANTS ON RADIATION PROTECTION

Yositeru Nakamura

Marine algae have acquired increasing importance in radiation protection, based on their ability to concentrate metal ions and radionuclides from sea water. This outstanding ability to accumulate radionuclides from water has even been suggested as a means of detecting local contamination of sea areas by assaying radioactivity in marine plants (*1*). The ability of brown algae to take up radionuclides is based on the chemical reaction of an intercellular substance composed of the salts of an acidic polysaccharide—alginic acid.

Alginates prepared from seaweeds suppress the intestinal absorption of radioactive strontium in many animal species and in man (*2–5*). This was originally found by the McGill group working with rats, but it has been confirmed since by other groups of investigators not only in rats, but also in cats, pigs, and in human subjects. The binding of strontium by alginate is basically an irreversible ion exchange process. It appears to be highly selective as calcium binding does not occur to a degree sufficient to interfere with dietary requirements. No untoward side effects have been observed after feeding the alginate preparation over a long period of time. Particularly interesting is the recent finding of Stara that alginate compounds are capable of reducing deposits of radiostrontium in bone by 20 percent through binding strontium resecreted into the gut (*6*).

Almost all of the brown algae belonging to the orders Laminariales and Fucales are alginophytes resources. The members of these orders show their maximum development in colder waters, and the main areas of their distribution are circumpolarly located in the Arctic and Antarctic regions. Their distribution extends to the regions where cold ocean currents sweep along the coasts. On the other hand, *Sargassum* and other members of the Fucales and certain members (for example, *Saccorhiza*) of the Laminariales, however, are characteristic of the subtropical or tropical regions (*7*).

In the Northern Hemisphere, species of the genus *Fucus* are abundant in northern temperate waters and are associated with the genera *Pelvetia*, *Ascophyllum*, and *Himanthalia*. The Fucales also show an extensive development in the Southern Hemisphere, and various distinctive genera (*Xiphophora*, *Notheia*, *Hormosira*) are recorded from Australia and New Zealand.

Typical of the Laminariales of the northern hemisphere are the Chordaceae, Laminarieae, Alarieae, and Agareae. The *Laminarias* are essentially northern in their distribution. The Pacific coast shows a considerably greater diversity of forms than does the Atlantic and both on the Asiatic and American shores, members of this order extend far towards the south, although the two floras are in part different. *Undaria* appears to be confined to Asia, while along the American shores are found *Postelsia*, *Pelagorphycus*, *Nereocystis*, *Egregia*, and so forth. The characteristic Laminariales of the Southern Hemisphere are *Lessonia*, *Ecklonia*, and *Macrocystis*. *Macrocystis pyrifera* has the widest distribution of all the species of Laminariales. Its area extends over the whole of the southern subantarctic zone. It follows the cold Humboldt current up to western shores of South America near Callo, Peru, and extends along the western coast of North America from Magdalena Bay to the Monterey Peninsula.

Quantitative surveys of the brown seaweed resources have been carried out in various countries. To the best of my knowledge, the estimated total amount of alginophytes in the world excluding *Sargassum* is about 48 million tons (*8*). In Scotland the standing crops of *Laminaria cloustoni*, *L. saccharina*, and *L. digitata* along the whole coast are estimated about 10 million tons from a preliminary survey by means of aerial photography. The total kelps available in British Columbia waters, such as *Macrocystis*, *Nereocystis*, *Laminaria*, *Alaria*, and *Hedophyllum* are estimated by Scagel to be at least 1.5 million tons (*9*). Three to 20 times this amount have been suggested by others. On the Pacific coast of the United States, the standing crops of *Macrocystis*, *Nereocystis*, and *Alaria* are estimated to be about 32.5 million tons.

In Japan, the standing crops of the alginophytes along the whole coast of Hokkaido Island (12 species of the Fucales and 15 species of the Laminariales) are estimated about 1.5 million tons, exclusive of *Laminaria* and *Undaria* used as food (*10*). The mean annual productions of *Laminaria* and *Undaria* in Japan are about 150,000 and 50,000 tons, respectively. The standing crops of other alginophytes of Japan, *Ecklonia* and *Eisenia*, are estimated to be at least about 100,000 tons.

If large quantities of seaweed products are required for radiation protection, some methods of marine culture or farming must be developed so that alginates with specific properties can be prepared. Experience in the cultivation of certain seaweeds has already been gained in Japan.

In the coastal seas of Japan, propagation of edible brown seaweeds, such as *Laminaria* and *Undaria* and the agarophytes (*Gelidium*), is made by planting stones or concrete blocks, or by blasting out rock surfaces with explosives to make new substrata. These methods of propagation of seaweeds have been adopted by fisheries cooperative associations with the financial aid of the Japanese Government since 1951.

Seaweed cultivation, especially *Porphyra* cultivation, is carried on extensively along the Pacific coast of Japan from Hokkaido to Kyushu. Currently the cultivation of *Undaria* with ropes fixed to rafts is carried on and is becoming popular among fishermen. A similar method for *Laminaria* cultivation is being tentatively tried in Hokkaido.

An improved technique for laboratory culture of brown algae has been developed in our laboratory (*11*). The use of the ESI medium and the control of temperatures and photoperiods make it possible to grow, unialgally, a number of species of brown algae into the adult stage in glass test tubes and to continue the culture from generation to generation. This new culture technique not only promises us light on our present scant knowledge of the life history, ecology, physiology, and genetics of seaweeds, but also will give us much information towards developing new techniques of their cultivation in the sea.

Studies on the resources of brown algae and the development of cultivation technique acquire new importance in view of the demonstrated ability of these species to sequester dangerous radionuclides. The finding of the protective effect of marine plants is probably the most important recent advance made in radiological health.

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EDUCATION AND TRAINING FOR A PEACEFUL NUCLEAR WORLD

Benjamin H. Bruckner

Accelerating advances in peaceful applications of nuclear and radiological sciences and technology present promises and formidable challenges, technically and educationally. Significant developments are foreseen in radiological sciences and in applications of nuclear power and radioisotopes in industry, agriculture, commerce, government, medicine, scientific research, and many other areas of human endeavor. In nuclear power generation, the United States, which today has an operating plant capacity of about 2 million kilowatts, is projected to have in the year 2000 a capacity in excess of 700 million kilowatts (fig. 1) (*1*).

The implications are awesome, for benefit and possible associated risk, of such vast quantities of nuclear power with attendant fuel production and recovery plants and environmental and waste disposal problems.

The need for more qualified people to participate in and enhance well-ordered radiological progress is recognized in responsible quarters, both public and private. The medical use of radiation, including x radiation is among the more important sources of human exposure today (*2, 3*). The requirements for radiation protection and health manpower have been considered in detail by experts and are discussed explicitly in the report of the National Advisory Committee on Radiation (NACOR) of April 1966 entitled "Protection and Improving Health Through the Radiological Sciences" (fig. 2) (*4*). Implementing the recommendations, the Public Health Service is making extensive efforts to produce the scientists and technologists needed for the efficient and safe use of radiation in medicine and the allied areas.

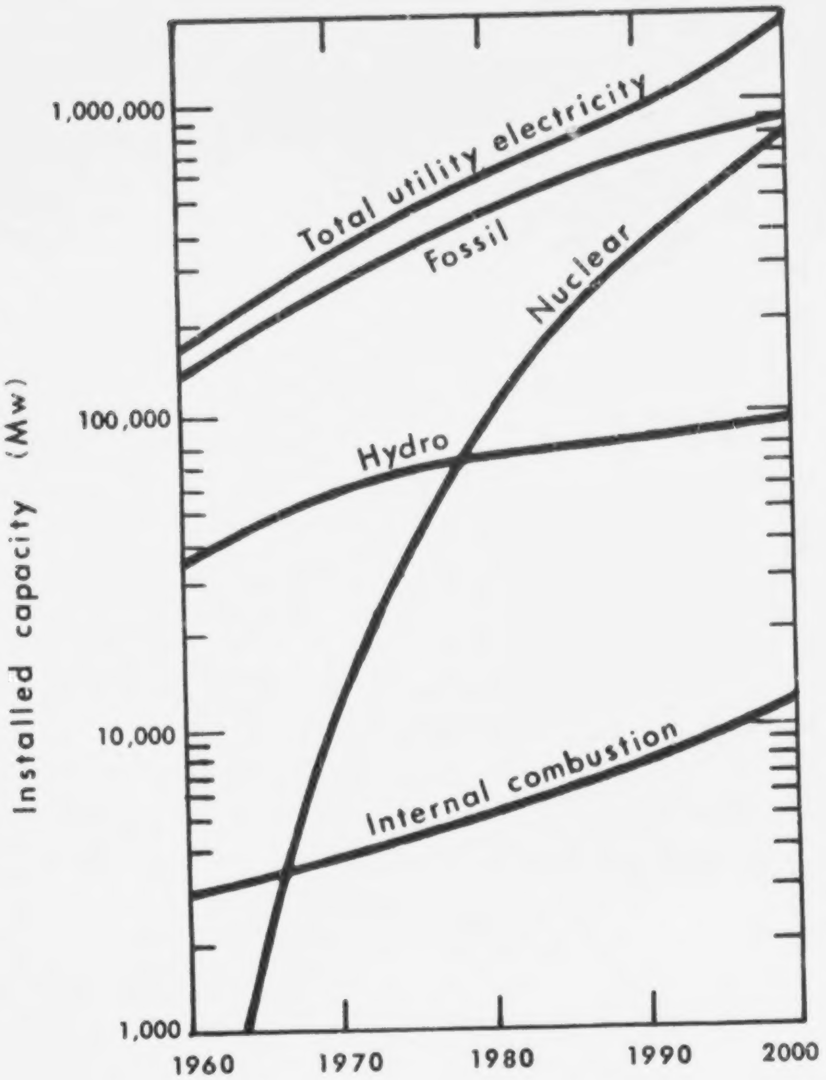

Figure 1. Electric utility generating capacity (*1*).

Health problems related to radiological advances are of concern not only to the the medical profession primarily, but to everyone generally, since through their environmental factors they have acquired economic, political, and social significance.

Peaceful applications of nuclear developments have social objectives. This fact may also be deduced from consideration of the principle, which is accepted as Federal policy, of weighing the benefits versus the risks of applying ionizing radiation to constructive purposes consistent with the preservation and advancement of public health (*2*). An examination of this principle makes it apparent that subject matter areas of benefit may be quite removed from those of the associated possible risk; and that the human populations to be benefited, in any specific instance, may be different from those subjected to the cor-

Training Programs Required in Radiological Sciences
(NACOR 1966)

Professional		Technological
Physicians	Scientists and Engineers	Technicians
Radiologists	Radiochemists	X-ray technologists
Clinical	Radiobiologists	Radiation therapy technicians
Academic	Radiological physicists	Nuclear medicine technicians
	Radiological engineers	
	Radiological health specialists	

Figure 2. Training programs required in radiological sciences (NACOR 1966).

responding possible risk. Moreover, the "weighing" process, which may require the advisory services of the most highly knowledgeable and wise counselors in the social as well as the physical sciences, may not be clear cut. These considerations require the most sophisticated and profound educational preparation and understanding.

Education is properly concerned with the bases of knowledge: not so much *what* one knows but *how* and *why* one knows. The formal educational process should include science rightfully grounded in epistemology. The introduction of a child in elementary school to science as it really is—an experimental experiential endeavor—should be a heuristic process, and a smooth natural component of his developing education. Probably one of the more formidable problems is the education of elementary school teachers to recognize, accept, and teach science as one of the liberal arts. The current gentle movement in this direction hopefully will grow as more technical men of vision such as the Nobel Laureates, I. I. Rabi and G. T. Seaborg emphasize the philosophic basis of science and ally themselves with professional educators in curriculum and program development (*5, 6*). Nuclear science and technology must also be built into the academic curricula at all levels, junior and senior high schools, and in research.

Nuclear science, as a component of all science, is expanding in size, scope, depth, and strength. The educational needs are enormous. Formal scientific education takes longer today than ever before. The facilities and apparatus needed for modern nuclear science and technology are far more complex and expensive than those required just a few years ago. For necessary support and orderly development, it is highly advantageous that administrative and fiscal decision makers have better than a superficial understanding of nuclear science, as well as the most immediate contact with the nuclear knowledgemakers.

A precedent for peacetime governmental support of graduate education was established in 1945–1946 by the Manhattan Engineer District of the U.S. Army Corp of Engineers (the wartime forerunner of the USAEC). Continuing legislative and administrative developments have resulted in full acceptance of Federal support of nuclear education and training.

Within the U.S. Department of Health, Education, and Welfare, this function is covered generally in the Public Health Service Act of 1944. Whereas three activities contribute chiefly to radiological health sciences training, the Bureau of Health Manpower, the National Insitute of General Medical Sciences, and the National Center for Radiological Health, the NCRH has the overall program responsibility for training and developing radiological health sciences personnel, on the State, National, and local levels (fig. 3).

This responsibility is carried out by the Training and Manpower Development Program of the NCRH through its three principal activities: Institutional Training Grants to established educational institutions to train specialists and technicians; intramural short-term training services to provide short courses, seminars, on-the-job training and the like, consultation, counseling for the purpose of developing new workers, and providing specialized job-related training; special projects supported by outside contracts and intramural efforts designed to provide and to develop radiological health sciences people to use radiation efficaciously and safely.

The education and training goals for a peaceful nuclear world properly have a three-phased priority order, immediate, intermediate, and long range.

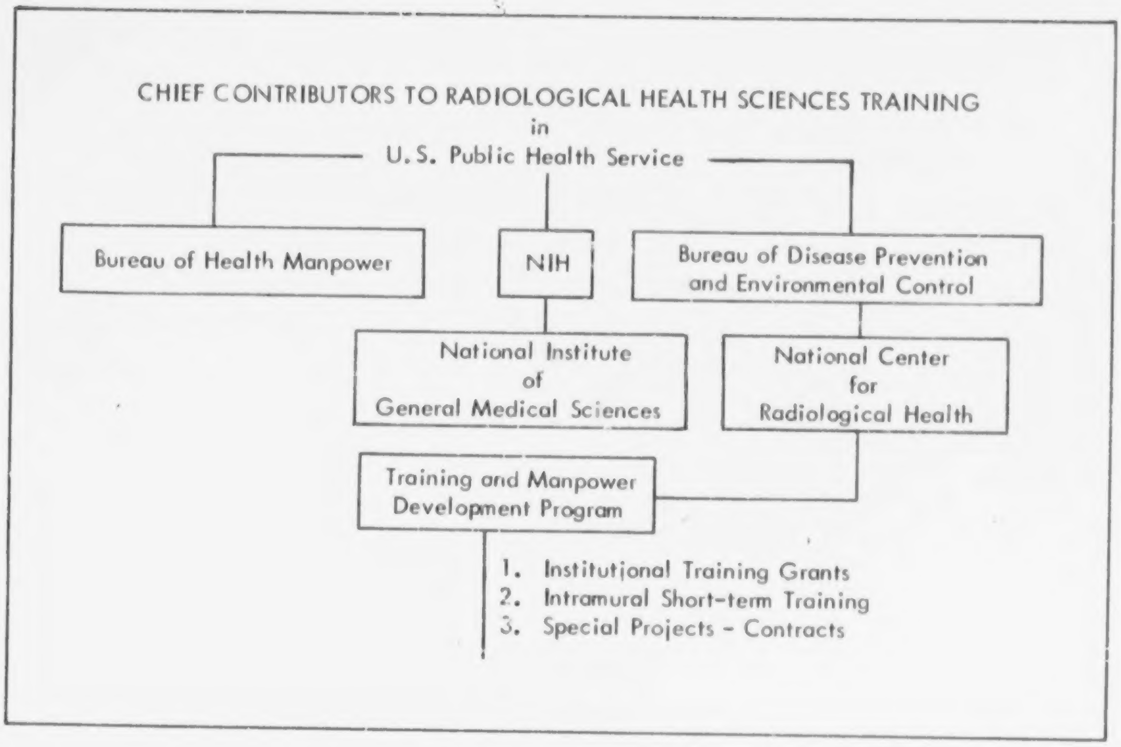
CHIEF CONTRIBUTORS TO RADIOLOGICAL HEALTH SCIENCES TRAINING
in
U.S. Public Health Service
Bureau of Health Manpower
NIH
Bureau of Disease Prevention and Environmental Control
National Institute of General Medical Sciences
National Center for Radiological Health
Training and Manpower Development Program
1. Institutional Training Grants
2. Intramural Short-term Training
3. Special Projects - Contracts

Figure 3. Chief contributors-to-radiological health sciences training in U.S. Public Health Service.

On the immediate level, probably the quickest results may be obtained by making better and more efficient use of personnel already in the field. Short-term courses and on-the-job training designed for specific job functions can be most effectively used when combined with winnowing out of semiprofessional and subprofessional tasks from existing professional positions, so as to free professional workers for truly professional activities and to delineate better the necessary subprofessional functions. Many modern machines and pieces of apparatus have become so reliable and efficient that it is no longer necessary to have professional-level operators. At the same time, quality control and performance testing needs increase professional staff requirements. The intermediate level of priority clearly involves training and retraining, for which the necessary background research, knowledge, and skills are yet to be accomplished. This should include the updating of obsolete and obsolescent skills, the tapping of new sources of manpower, such as the handicapped and disadvantaged groups, and the retraining of workers who may have left the field (for example, retired workers, married women). Of course, adequate incentives have to be provided to interest prospective employees and retain those already in the field.

On the long-range level, education rather than training must be emphasized to encourage more young people to enter careers in nuclear sciences and technology, to stimulate undergraduate and graduate education and research, and to expand public knowledge and awareness of nuclear matters.

Although education is a relatively long-range process, there is an urgency for coming to grips with the problem. We are increasingly aware that the continuously changing interaction between man and his environment, through the very processes of living, may result in potential injury and disease. For orderly and effective development we must proceed, imaginatively, deliberately, and now.

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PART III: SOURCES OF RADIATION AND EPIDEMIOLOGY

Chairman: E. A. Watkinson

Natural Radiation
Christopher R. Hill

Dosimetry in Relation to Epidemiology
L. D. Marinelli

The Symptomatic and Haematological Disturbance Following Total Body Radiation of 300-Rad Gamma-ray Irradiation
W. D. Rider and *R. Hasselback*

Epidemiology of Late Effects of Radiation in Man
Albert W. Hilberg

Radiation Accidents
George E. Thoma, Jr.

Industrial Exposure to Radiation
John C. Villforth and *Richard F. Boggs*

Environmental Contamination From Atomic Plants
Collin A. Mawson

Changes Induced by the Irradiation of Nutritional Elements
Roger Ghys

NATURAL RADIATION

Christopher R. Hill

A fairly detailed description of man's normal natural radiation environment is now possible and this has been well summarized by UNSCEAR as presented in table 1.

Table I. ***Dose rates because of external and internal irradiation from natural sources in "normal" areas***

Source of irradiation	Dose rates (mrad/year)		
	Gonads	Cells lining bone surfaces [a]	Bone marrow
External irradiation:			
Cosmic rays:			
Ionizing component	28	28	28
Neutrons	0. 7	0. 7	0. 7
Terrestrial radiation (including air)	50	50	50
Internal irradiation:			
Potassium 40	20	15	15
Rubidium 87	. 3	<. 3	<. 3
Carbon 14	. 7	1. 6	1. 6
Radium 226		. 6	. 03
Radium 228		. 7	. 03
Polonium 210	. 3	2. 1	. 3
Radon 222 (dissolved in air)	. 3	. 3	. 3
Total [b]	100	99	96
Percentages from alpha particles and neutrons	1. 3	4. 4	1. 4

[a] The dose rates under this heading were actually calculated for the Haversian canals of bone. Doses to cells lining bone surfaces may be somewhat lower than those quoted here.

[b] Totals have been rounded off to two significant figures.

It will be the purpose of this paper to examine the "conventional wisdom" as represented by the above data, from the point of view of the areas in which a significant degree of uncertainty may still exist. Such uncertainty arises because of three separate factors:

1. Inadequacies in measurement technique;
2. Radiobiological interpretation (in relation to QF and DF); and
3. Variations between different population groups.

These factors can be considered separately and may each provide some indication of desirable future lines of research.

Measurement Techniques

Two components of natural environmental radiation on which fully satisfactory measurements have not yet been carried out, because of inadequacies in technique, are the heavy particle component of extraterrestrial (cosmic) radiation and the short-lived alpha emitters.

1. Cosmic-ray Heavy Particle Component:

The significance of this source of environmental radiation dose has only rather recently been generally appreciated. In physical terms it consists of a cascade of secondary nucleons that give rise to a series of spallation events both in the air and in tissue. Tissue dose arises from both the charged particles and the fast neutrons produced by such spallations. Difficulty in measurement arises because of the very small magnitude of the heavy particle flux relative to the background of low LET radiation and also to residual alpha contamination in detectors. Virtually no experimental information is yet available on such effects as shielding by overlying tissue and by building structures.

2. Short-Lived Alpha Emitters:

Almost all our knowledge of dose from internal alpha emitters is derived from autopsy measurements, which inevitably entail delays of several hours, if not days, post mortem. Measurements are, in practice, made only on longer-lived radionuclides, and the extent and distribution of the dose that arises from, for example, the lead 214—bismuth 214—polonium 214 decay chain has generally been ignored for lack of experimental data.

Radiobiological Interpretation

In discussing the significance of natural radiation, and particularly in making comparisons with artificial radiation sources, it may not always be appropriate to apply directly the conventions of radiological protection. An important instance of this is in the assignment of a value of RBE or Q.F. to the high LET component of natural radiation. Another problem of interpretation arises in considering inhomogeneities in distribution of internal emitters.

CHOICE OF RBE VALUE

In recent years a number of reports have been published indicating that, in certain experimental systems—some of them mammalian—the limiting value of RBE for alphas and fast neutrons, at very small dose rates, may be in the region of 20 to 50. Referring to table 1, it will be seen that such a situation, if confirmed, would have important implications, both as to the relative importance of the various components of natural radiation and in any comparisons of natural and artificial radiation sources.

INHOMOGENEITIES IN DISTRIBUTION

A suggestion that, rightly or wrongly, has aroused considerable concern recently is that polonium 210, deposited on bronchial epithelium as a natural volatile combustion product of tobacco, may give rise to significant radiation dose in certain discreet regions of epithelium. Since it has now been established that the total amount of this radionuclide present in an average smoker's lung is in fact very small, the problem has resolved itself into the dual question whether appreciable inhomogeneities in distribution do exist and, if they do, whether alpha particle dose delivered in this way would constitute a greater hazard than the same dose delivered quasi-homogeneously.

Variations Between Different Population Groups

Although so-called "normal" levels of natural environmental radiation dose are now established, comparatively few data (when set against those on strontium 90 and cesium 137) are available on the extent of its variation. Such variations as occur are mainly in three components: cosmic, terrestrial alpha, and internal alpha radiation, and variations in the magnitude of any one of these by factors of between 10 and 100 are not uncommon. It is of interest that variations in artificial radiation levels may be paralleled by natural levels, a case in point being the high cesium 137 levels in the Far North where an entirely analogous elevation in polonium 210 is also found to occur.

In order to be able to predict the existence of further population groups showing elevated internal alpha dose, additional information on the metabolic properties of the various radionuclides involved will be required.

The early hope, that a study of human populations subject to varying levels of natural radiation might indicate a relationship with patterns of disease incidence, has so far been unfulfilled. The reasons for this are threefold: inadequacy of statistics in many of the interesting (but often primitive) groups; the limited size of many of the groups; and the existence of differences, in factors other than radiation level, between exposed and control groups.

DOSIMETRY IN RELATION TO EPIDEMIOLOGY

L. D. Marinelli

Concern with the impact of the ever-expanding applications of nuclear fission to everyday life has focused worldwide attention on some recent epidemiological studies, and, in particular, on their quantitative rather than their qualitative conclusions. The attention is well deserved since they have furnished international bodies, such as the International Commission on Radiological Protection (ICRP) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), with the data necessary to evaluate some radiation risks in dosimetric terms, such as osteosarcoma and leukemia incidence per man-rad per year.

Events of the last decade involving this controversial field suggest that estimates of radiation risks become more convincing to the layman when they are related to human experience and less abhorrent to the radiobiologist when epidemiological deductions find confirmation in the laboratory animal colony.

Radiation dosimetry has played, and will continue to play, an essential role in the necessary interplay between laboratory and field observations, since its basic task is the same in both types of investigation; namely, the task of supplying a measure of the atomic events initiating biochemical and cellular perturbations, which lead ultimately to the observed effect.

Concern with the specification of dose, however, should include detailed information on the modalities of its administration, and should not detract from the importance of describing accurately the status of the populations under comparison. The latter requirement becomes especially important in studies at low doses of radiation, when the influence of extraneous factors can easily obliterate the observation of a true radiation effect.

It is conceded that the ultimate accuracy in the evaluation of dosimetric factors in radioepidemiology should be comparable to that attainable in the description of biological effects; that is, it need not be as high as that required in medical uses of radiation.

However, the attainable accuracy of the doses relevant to epidemiology depends not only on the precision of technical measurements, but also on the uncertainties introduced by variations in physiological and/or anatomical factors of the populations under scrutiny and, where applicable, also on additional uncertainties connected with sampling.

The technical approach to dosimetry varies considerably depending on whether the dose is due to internal or external radiation. With internal emitters the basic data require both radioactive and metabolic measurements, but the techniques vary somewhat with the study in question; thus in cases of luminous dial painters, the radium burden is assessed by whole-body counting, analysis of exhaled radon, and the measurement of excreta. It is then converted into rads by means of extensive autoradiographic and radiochemical analysis. Long-term metabolic parameters that describe the change of radioactivity with time have been obtained from studies of patients previously treated with known amounts of radium 226 a few decades ago. In the case of the radium dial painters, as in other industrial exposures, the magnitude of the initial intake is unknown and may vary widely; hence the measurement of every individual under observation is necessary.

In the Midwest Epidemiological Survey, which is concerned with the effects of a few picocuries of radium in potable water supplies in a population of about a million, the dosimetric problem is theoretically relegated to the measurement of radioactivity of water and food, since the metabolism of radium in man is fairly well known (*1*); however, the influence of population stability, the use of water softeners, and other epidemiological, demographic, and socioeconomical factors remain to be evaluated by judicious sampling.

In another study involving thorium dioxide in colloidal form, documentation of the diagnostic techniques used in given institutions seems adequate for the estimate of the intake pertinent to various categories of patients; however, some radiobiologically essential dosimetric measurements, which depend upon detailed assessments of radioactivity throughout the body, still pose a sharp challenge to the investigator, mainly because the most energetic members of the chain that translocate in the body have inconveniently short natural lifetimes.

It is important to stress at this point that operational difficulties in the analysis of cause and effect of thorium dioxide in man should stimulate rather than depress the meager measure of financial support that has been devoted to this epidemiological area. The present indecision in this regard recalls the official doubts that were expressed 20 years ago about the usefulness of the ABCC studies and the indifference that for almost a decade prevailed in many laboratories *vis-a-vis* the experimental study of effects of inhaled radioactive gases and particles. The direct relevance of epidemiological studies of thorium dioxide patients to the topics of this conference can best be illustrated by perusal of table 1 where the yearly dose rates of alpha radiation absorbed by various tissues of the typical Thorotrast patient are shown (*2*). It will be noted that, besides the well-known high levels accruing to the liver and spleen, dose rates of current concern accrue also to marrow, lung, and bone. As a rough guide, a fair mental picture of equivalent photon or beta radiation can be had by multiplying these values by 5 in order to account for a RBE of 10 and an average injection of 25 cc. It is obvious that in the case of the marrow and the lung, we are dealing with average dose rates in rems that are respectively 24 and 4 times the maximum levels considered to be permissible to those tissues by the ICRP. For obvious reasons, it is important to note that preliminary results indicate that in a pool of about 2,000 persons at risk for an average of 25 years, the leukemia incidence rate is roughly seven times normal (table 2). The average radioleukemogenic risk in this group is of the order of 1.8 cases per million man-rad-years. This figure should be compared to those mentioned by UNSCEAR and ICRP involving the Japanese survivors and the spondylitics, which are shown in the first two lines of table 3 (*7*).

Despite the obvious uncertainties owing to statistics and the rough estimates of years at risk, it is useful to gather some of these epidemiological figures in one table not so much to reach firm conclusions but to consider what we may learn from studies of this type. In table 4, by similar calculations, are gathered the epidemiological results on risk of osteosarcoma and leukemia from high and low LET radiation delivered at high- and low-exposure rates. Obviously the separation of the effect of the two variables has not been achieved, but of tantalizing interest is the fact that the ratio of the leukemogenic to the osteosarcoma risk seems to be of the order of 5 for the combination of high dose rate and low LET radiation, but it could be only 0.5 for low dose rate, combined with high LET irradiation. Of peripheral interest is the fact that if the natural incidences of osteosarcoma and leukemia were all attributed to background radiation, one would obtain ϵ_0 and ϵ_1 values of 1.4 and 14, approximately.

Of equal interest and perhaps of greater urgency should be an estimate of the doses to various parts of the lung of these patients who

Table 1. ***Maximum dose rates per 50 cc Thorotrast injection rads year^{-1}***

Element	$T_{1/2}$	*K* [a]	Liver	Spleen	Marrow	Bone	Kidney	Lung	Blood	Soft tissue
Thorium 232	$1.4\ 10^{10}y$	74. 5	44. 0	66. 0	7. 4	0. 007	0. 35	0. 5		
Radium 228	$5.8y$									
Thorium 228	$1.90y$	100	26. 3	34. 0	5. 0	. 30	. 2	. 7	0. 08	0. 14
Radium 224	$3.64d$	105	30. 2	34. 5	2. 1	. 63	. 68	. 2	. 22	. 04
Thoron + *ThA*	51s; .16*s*	234	36. 0	43. 0	5. 5	1. 31	1. 5	6. 9	1. 96	. 07
ThB (Lead 214)	10.6 hr									
Bismuth 212 (*Thc*)	1 hr	38	2. 8	4. 0	. 9	. 21	. 4	1. 0	. 50	. 05
Polonium 212 (*ThC'*)	$.3\mu s$	109	8. 2	11. 4	2. 7	. 61	1. 1	3. 3	1. 42	. 15
Thallium 208 (*ThC''*)	$3m$									
Total		---	147	192	23. 6	3. 1	4. 2	12. 6	4. 2	0. 45

[a] Rads per year per nCi/gram.

Table 2. *Approximate radioleukemogenic risk ϵ_L in Thorotrast series*

N = population
Tr = years at risk

$\dot{D}$ = rads y^{-1} $\simeq$1/2 ml inject.
n_L = cases of leukemia

$\epsilon_L = 2n_L/\dot{D}\,N\,Tr^2$
(leukemia)

Source	N	Tr	$\dot{D}$	n_L	$\epsilon_L \times 10^6$ [a]	Reference
Denmark (Faber)	514	25	10. 7	6	3. 1	(*3*)
Sweden (Blomberg et al.)	436	23	8. 8	1	0. 9	(*4*)
Portugal (Da Silva-Horta et al.)	930	26	13. 1	9	2. 0	(*5*)
Japan (Takahashi)	187	26	15(?)	1	1. 3	(*6*)

Average: For $\sim 5 \times 10^4$ man year, no. of leukemias expected: $5 \times 10^4 \times 50 \times 10^{-6} \simeq 2.5$—cases found: 17 or $\sim 7\times$ normal.

[a] Average whole group $\epsilon_L \simeq 1.8$.

Table 3. *Radioleukemogenic risk ϵ_L from external sources*

D = Total rads
D = Rads y^{-1}

ϵ_L = Leukemia/10^6 man/rad/year

Source (radiation)	D	D	ϵ_L	Reference
A.B.C.C. γ + neutrons	300	$>10^{13}$	1. 6	(*7*) UNSCEAR (1964) p. 84.
Spondylitis (x rays)	850	$\sim 3.2 \times 10^6$	1. 3	(*8*) Court-Brown et al. (1965).
Children in utero (x rays).	1–10	$\sim 10^7$	>5.0	UNSCEAR (1964) p. 89.
Radiologists [a] (x rays)	[b] 600†	[b] 15	[b] 0. 5	UNSCEAR (1964) p. 85.

[a] Protracted irradiation.

[b] May vary by a factor of 3 either way.

exhale a considerable amount of thoron. Doses to various sections of the lung, as calculated by Muth and Grillmaier (*9*), are shown in table 5 and compared to similar calculations by Jacobi (*10*) on doses resulting from one WL (Working Level) atmosphere in mining operations. In view of the various uncertainties inherent to calculations of this sort, no great claim for accuracy can be made, especially for the various tracts of the respiratory tree, but the comparison has the merit of being based on similar physiological, diffusion, and attachment constants. I may add that one assay of thorium bromide in the lung made in our laboratory yielded 12 rads per year for the average dose to alveoli and bronchioli; namely, a value embarrassingly close to these figures (*11*). On an average of 25 years at risk, these patients have accumulated roughly an equivalent integral exposure of the order 1,500, 3,000, 40, and 2,100 WLM (Working Level Month), respectively, in the alveoli, small bronchi, large bronchi, and trachea;

Table 4. *Approximate oncogenic risk* ϵ *in cases per* $10^6 \cdot y^{-1} \cdot (man\text{-}rad)^{-1}$

	ϵ_0 = osteosarcoma		ϵ_l = leukemia	
Dose rate	High-LET α-Radiation		Low-LET Electron-Radiation	
	ϵ_0	ϵ_l	ϵ_0	ϵ_l
High	?	?	0. 23 (*Sp*)	1. 5 (*Sp*) (*J*)
Low	? (*T*) 4. 0 (*D*)	1. 8 (*T*) 1. 8 (*D*)	? (*J*) ? (*R*) [$<$1. 4] (*B*)	5. 0 (*f*) 0. 5 (*R*) [$<$14. 3] (*B*)

(*Sp*) = Spondylitis (*8*).
(*J*) = Japanese survivors (7).
(*T*) = Thorotrast pts. (*B*) = Background.
(*f*) = Fetal irradiation.
(*R*) = Radiologists (7).
(*D*) = Dial painters (radium 226) (7).

that is, doses wholly comparable to those experienced by the mining population mentioned in FRC Report No. 8 (*12*).

An inquiry into the incidence of bronchogenic carcinoma in Thorotrast patients was made by Faber (*3*) as far back as 1961, and he concluded that the number of cases observed in the Danish material was the number to be expected taking age, sex, and time of observation into consideration. As of today, if one considers all the cases collected by Da Silva-Horta (*5*) and Okawara (*13*) (the latter includes the cases of Faber) as pertaining to the population of 2,000 considered in table 2, one calculates an incidence of 13 cases in roughly 30,000 to 50,000 man-years. This figure is certainly not from 8 to 46 times the normal expected incidence, which according to FRC Preliminary Report No. 8 is the case for the mining populations exposed to comparable doses of radiation to the respiratory tract. It is obvious, then, that these data are relevant to any inquiry as to the causation of bronchogenic carcinoma in underground uranium mines, and that further study along these lines needs the immediate support of the agencies concerned and the attention of the best epidemiologists and radiological physicists. (As to the role of the α-irradiation of the respiratory track caused by smoking (*14*) it is pertinent to note that Da Silva-Horta (*5*) found no bronchial carcinomas in 331 Thorotrast injected females and 5 cases in 590 males.)

After this detailed demonstration of the necessity of sharpening our skill in the radiation dosimetry of internal emitters, we turn to offer some comments on the assessment of the relevant external dose in epidemiology that presents a spectrum of difficulties and uncer-

Table 5. ***Dose rate to lungs***

Exposure	Tissue external radiation	Millirads per year				Rems $-y^{-1}$		
		α-Radiation				Quality factor		
		Radon 222+*d*	Thorium 228+*d*	Internal [a]	Total α	1	10	100
Mining operations [b]	Alveol. 5,000	720	----	20	740	5. 7	12. 4	790
100 pCi/1 Rn+	Bronch. 5,000	720	----	20	740	5. 7	12. 4	790
100 pCi/1 daughters	Brouch. (SQ) 5,000	21, 000	----	20	21, 000	26. 0	215	2, 100
	Trachea 5,000	3, 800	----	20	3, 800	8. 8	43	385
50 cc Thorotrast [c]	Alveol. 115		8, 000	----	8, 000	8. 0	80	800
3.6×10^4 pCi radon 220 min^{-1}	Bronch. 115		16, 000	----	16, 000	16	160	1, 600
–	Bronch. (SQ) 115		5, 500	----	5, 500	5. 5	55	550
	Trachea 115		55, 000	----	55, 000	55	550	5, 500
Cigarette smoker [d]	Bronch. 115	6. 6	----	----	6. 6	----	6.6 min.	
	Epithelium	----	----	----	----	----	40 max.	

[a] One-fourth average dose to osteocytes (20 percent versus 80-percent retention at continual intake).

[b] From Jacobi (table $5\times40\times168^{-1}\times10$).

[c] Muth and Grillmaier, Vienna, October 4-7, 1965.

[d] From Radford et al. on Polonium in Cigarettes.

tainties wider, perhaps, than those just mentioned. On one extreme, one has the relatively easy task of assessing effects resulting from clinical irradiation. In these cases the investigator has all the factors and records necessary to establish, with more than sufficient accuracy, the exposure to a given anatomical field. From this information, using classical methods of radiological physics, the average dose to a given organ can be satisfactorily determined. Clinical records in representative institutions have successfully extended these estimates to 10^7 to 10^8 persons, as exemplified by the various surveys concerned with the average significant genetic dose to entire national populations. It is hoped that similar techniques will be employed on an international scale to calculate the incidence of late morbidity per man-rad year in patients successfully treated for cancer of the cervix and to obtain, at relatively low cost, a reference point on the effects of irradiation of a well-defined portion of the body to compare directly with the effects observed on irradiated spondylitics. It should be recalled, however, that contrasted to the relative ease with which absorbed dose can be evaluated—radioepidemiological studies based on clinical exposure face the dilema of either choosing control populations of identical medical status not having been exposed to radiation, or of establishing beyond doubt that whatever the immediate cause leading to irradiation, the irradiation only (and not the cause itself or its therapy) is responsible for the effects observed at a later date.

In the study of dose, circumstances change somewhat because of background radiation. Technically, difficulties arising from the smallness of the dose can be easily overcome by employing suitable organic scintillators, but the difficulty is shifted to the task of "sampling" the background exposure of the population in question. At last report our colleagues in Brazil seem to have coped with this problem by the judicious use of inconspicuous personnel dosimeters (*15*).

The sampling of the dose to a population becomes of itself difficult to implement when the source and/or the circumstances of exposure cannot be reconstructed. In this classification falls the calculation of the dose to the survivors of Hiroshima and Nagasaki. These dosimetric studies must evaluate the dose delivered to tens of thousands of individuals by radiation emanating from an asymmetrical, irreproducible source of neturons and gamma rays whose flux is subject to the inverse square law of distance, and to attenuation and scatter by the atmosphere and walls of different composition. The latest dosimetric report augurs well in this regard; however, since activation analysis of cobalt impurities in iron structures and utensils, and thermoluminescent measurement of roof tiles seem to be connected directly with the best estimates of radiation fluences of August 1945 and their azimuthal variations (*16*).

On the other extreme, we face the less expensive, but perhaps more perplexing task of assessing the dose to the practicing radiologists of a few decades ago, on whom several epidemiological surveys have been, and, for good reason, are still being done. To assess the average marrow dose pertinent to the leukemia incidence of this population, it is necessary to obtain its dose-distribution function and only one function would be sufficient if the range of doses received within the entire group were small. It should be realized, however, that in this particular case, this range could be as high, or higher, than 1,000. To obtain a realistic appraisal of the leukemogenic risk of radiation, it is necessary to establish whether the average dose to the leukemia victims is not very different from the average dose to the rest of the population. The task appears tedious and demanding, but it may be accomplished, perhaps, if colleagues, technicians of the deceased, and the surviving members of the profession would contribute adequate information not only on the radiological armamentarium and techniques prevailing in the epoch of interest but also on the caution extant both in the profession in general, and in the leukemia group in particular.

In conclusion, I would like to stress the view that if we are facing a period of budgetary restriction in matters concerning radiological health, we should give a thoughtful look at priorities of support, especially at those studies involving long-term effects that cannot be postponed because of either natural extinction of the population or attrition of medical records, as in radioepidemiology. Mice and other laboratory animals will always be with us.

These decisions will require courage because, despite recognition of their valuable contributions by UNSCEAR and ICRP, radioepidemiological studies per se seem to be still the object of disdain on the part of certain coteries of investigators and administrators. Not extraneous to this attitude may be the human propensity to pursue the easiest path, unmindful of the urgency of the task and the conceit inherent in the philosophy that true scientific effort should ignore social needs. Certainly it cannot be logic. It has become abundantly clear that evaluation of radiation risks on man cannot be attempted within the foreseeable future without the aid of epidemiological study.

It is equally clear, also, that the interplay between laboratory and field observation is essential to the interpretation of epidemiological findings and to their extrapolation to different conditions of exposure, and that all this is impossible without dosimetric information.

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THE SYMPTOMATIC AND HAEMATOLOGICAL DISTURBANCE FOLLOWING TOTAL BODY RADIATION OF 300-RAD GAMMA-RAY IRRADIATION

W. D. Rider and *R. Hasselback*

My contribution to this symposium is limited and will only confirm observations of others—notably Court-Brown and Abbatt—about 15 years ago, but perhaps it is worth reiterating since it seems that their observations have been overlooked (*1*).

In the past 3 years, we have had occasion to treat about 20 patients with single exposures of total body radiation as part of the management of malignant disease. It is not the purpose of this paper to consider either the rationale or results of this form of treatment, but to use this experience as a contribution to this symposium.

This group comprises mainly children and adolescents afflicted with Ewing's tumor of bone; they were all in good general condition and had normal peripheral blood pictures and bone marrows. All were afebrile, thus, from the point of view of the effects of total body radiation, these individuals were as close to normal as one can justifiably irradiate. The symptomatic and haematologic response to the radiation in all these patients fitted a pattern with almost clockwork regularity. Several other patients who were seriously ill with malignant disease have been treated with total body radiation, but these have been excluded from this study since it is felt that their response bears little relation to the effects observed in the normal individual.

The radiation was carried out by the technique described by Cunningham and Wright (*2*)—a ceiling mounted cobalt 60 unit is used with a special collimator, and the source of radiation is scanned backwards and forwards over the patient at a source—skin distance of about 100 centimeters—both sides of the patient are treated and the dose estimated at the midplane position. The transmitted dose is measured in all instances as a check against calculations. With this technique the absorbed dose is homogeneous within ±10 percent limits, and is, therefore, much more homogeneous than the common practice of using very long source to skin distances in order to cover the patient with the beam of radiation. The dose delivered is 300 rads in about 15 minutes, and this puts it into the category of "acute radiation exposure." A small number of cancer patients who were in good general health have been irradiated with doses of 20 to 220 rads.

The symptomatic disturbance produced by this form of radiation, often called radiation sickness, is similar to that produced by larger doses of partial body radiation. The patients were not sedated since from past experience we have found that sedation only makes the nursing problem more difficult.

Following radiation there is an asymptomatic interval of 45 to 60 minutes, prior to the onset of vomiting, during which time the patients feel perfectly well and just cannot believe that they are likely to be sick. The vomiting begins suddenly and is not always preceded by nausea—it resembles the projectile vomiting seen in patients with raised intracranial pressure. The first episode lasts 15 to 20 minutes and is followed by a period of somnolence, indeed often deep sleep. During the ensuing 6 hours, periods of vomiting alternate with sleep and fatigue—the length of vomiting decreasing while the periods of sleep increase. The last phase of deep sleep lasts about 2 hours and after this the patients awake fresh and hungry. The clinical course is depicted in figure 1. By the next day patients are fit for discharge from the hospital and remain symptomatically well until the onset of symptoms associated with the pancytopenia at about the 25th post-radiation day.

Haematological changes similar to those observed in this study have been reported previously (*1*). The pattern is so similar in each instance that although the graph shown in figure 2 is a composite of six patients, almost all cases studied have followed an identical pattern. Analysis of the data in figure 2 reveals:

1. A constant granulocytosis occurs in the first 8 hours after radiation and amounts to a threefold increase in numbers over the baseline values. The granulocytes have returned to preradiation baseline values within about 30 hours.
2. A constant lymphopenia reaches its lowest levels in 8 to 12 hours. This lymphopenia persists until total haemopoietic recovery occurs at approximately the 35th post-radiation day.
3. No rise or fall in platelets is noted during the first 30 hours.

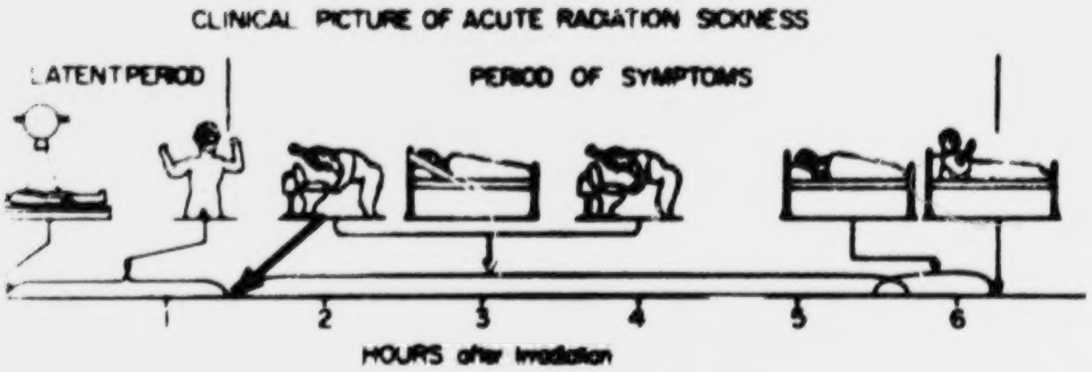
CLINICAL PICTURE OF ACUTE RADIATION SICKNESS
LATENT PERIOD
PERIOD OF SYMPTOMS
1
2
3
4
5
6
HOURS after irradiation

Figure 1. Clinical picture of acute radiation sickness.

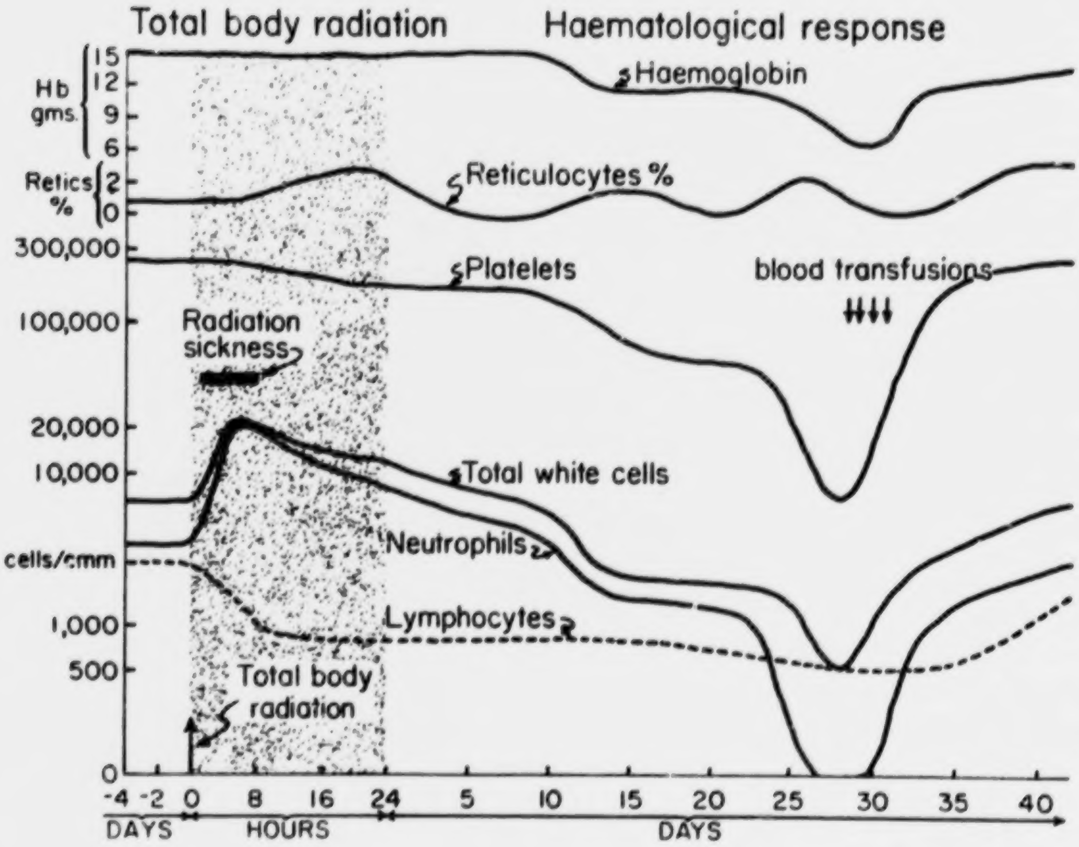

Figure 2. Haematological changes following total body radiation.

4. From the 1st to about the 10th day there is a slow and gradual decline of leukocytes, and from about the 12th to the 22d day there is a plateau.

5. From the 22d to the 27th day there is a rapid fall in leukocytes until, as a rule, only lymphocytes are to be found in the peripheral blood, and these usually amount to about 500 cells per mm^3.

6. Recovery is prompt after the 30th day and normal figures are reached within a week thereafter.

7. Platelets follow the leukocyte pattern after the 10th day.

8. The haemoglobin follows a general pattern of decline comparable to the shape of the fall in leukocytes.

9. No constant pattern of reticulocyte count has been observed.

The clinical pattern around the 25th day is one of pancytopenia. Most patients exhibited some degree of purpura, some had minor bleeding from the gums. Infection was not a real problem, but most patients ran a fever for a few days that responded to a broad spectrum antibiotic--blood cultures were rarely positive, and even throat swabs did not often show any specific organisms. In the management of this pancytopenia phase the cardinal rules have been:

1. Barrier nursing.
2. Treatment of infections as and when they arise—not prophylactically.
3. Simple blood transfusions to replace haemoglobin. Platelet transfusions have not been used routinely; however, on two occasions when platelet transfusions were used, the haemopoietic recovery was slower than the average.

The longest period of observation is now 3 years, and to date there is no evidence of haematological abnormalities. Chromosome studies of the lymphocytes have not been done.

In the whole group of patients submitted to this program of total body radiation only one did not fit the pattern described. This was a 9-year-old girl in whom a diagnosis of Ewing's tumor had been made and, at the time, presented a reasonably classical picture. After her total body radiation, however, she was much sicker than the others, ran a fever of 105° F. for 24 hours and was slower to recover. She reached her maximum haemopoietic depression at the 8th day but recovered satisfactorily and remained well for a year. At the end of a 1-year routine followup, haematology revealed that she was suffering from acute leukaemia, and this was supported by bone marrow study. When the biopsy material was reviewed, it was apparent that the original diagnosis was wrong. We were in fact dealing with a leukaemic infiltration of bone rather than Ewing's tumor. She had an excellent year's remission of acute leukaemia with one dose of 300 rads and currently is in remission with cytotoxic drugs.

When reviewing the fate of these patients, one is left with a distinct impression that those who had the most symptomatic disturbance were those who have fared worst. This might be a reflection of the extent of the occult disease at the time of radiation—those with the largest amount of tumor having the worst sickness and the most profound pancytopenia as was evident in the child with acute leukaemia.

A small number of other patients have been treated with lesser amounts of total body radiation, using the same radiation technique. From these results it can be stated that doses of 50 rads, 100 rads, and 220 rads do not produce radiation sickness, although at 220 rads nausea occurred at 3 to 4 hours after the radiation. The haemopoietic depression produced by 220 rads is similar to 300 rads but slightly less in degree.

One patient has on two occasions been irradiated to 200 rads. The first irradiation produced no sickness, and a haematological picture similar to but less marked than that described for 300 rads. The second irradiation 1 year later was divided into two fractions separated by an interval of 8 hours—this produced no symptomatic disturbance, and the haematological response was quite different. Practically no granulocytosis occurred and the leukocyte depression that occurred subsequently was minimal—the peaks and trough were smoothed out completely. This latter finding has been confirmed in two other patients in whom the 200 rads has been divided into two 100-rad fractions.

From this experience, and personal communications from others, we have been unable to correlate symptomatic disturbance and dose rate. It would appear that the absolute amount of radiation absorbed is of more significance than dose rate.

SUMMARY

1. Total body radiation of 300 rads in man produces a characteristic symptomatic and haematological response with little individual variation.
2. Vomiting occurs regularly 45 to 60 minutes after the radiation and persists for 6 to 8 hours.
3. Maximum haemopoietic depression occurs between 25 and 30 days after the radiation.
4. Haemopoietic recovery is rapid and is best handled by barrier nursing, antibiotics, and blood transfusions as indicated by the clinical situation.
5. No dose rate dependency can be demonstrated.

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EPIDEMIOLOGY OF LATE EFFECTS OF RADIATION IN MAN

Albert W. Hilberg

In preparation of my remarks concerning the epidemiology of late effects of radiation in man, I found that I had to ask myself just what does this title imply.

What precisely is epidemiology associated with long-term effects of radiation in man? I found that I, at least, had to define just what epidemiology is. Only when I could reach a satisfactory answer to this question could I then apply this discipline to late effects of radiation in man. MacMahon's (*1*) definition of epidemiology seems to me to be quite apt: "Epidemiology is the study of the distribution and determinants of disease prevalence in man." He states further that "distribution" is "descriptive epidemiology" and "determinants" is "analytic epidemiology." To clarify the definition, descriptive epidemiology is the "description of the distribution of disease, with comparisons of its frequency in different populations and in different segments of the same population." Analytic epidemiology is defined as "observational studies designed specifically to examine the hypothesis (tentative theories to explain observations in terms of casual associations) developed as a result of the descriptive study."

Since epidemiology is a science heavily devoted to descriptions of disease and disease patterns, it depends upon the observation that certain events seem to be associated in time. These associated events lead to the identification of characteristics that allow one to think in terms of cause and effect hypotheses. The first event is a cause that produces a following event. As MacMahon states, the use of this type of terminology "sometimes leads to the idea that the second event is the inevitable consequence of the first," and he continues that "This concept is now discredited by most schools of philosophy. There is nothing inevitable about causal associations." The longer such a relationship of events has existed the stronger is one's belief in the cause-effect relationship; but such belief is a result of empirical observation rather than logical deduction or true scientific evidence.

To complete these remarks concerned with what is epidemiology and to allow us to proceed, in the absence of experimental proof, to much of which is to follow, again I borrow freely from MacMahon et al. (*1*) to describe three types of considerations that are useful to explain the possibilities of cause and effect:

1. Time sequence; that is, the sequence of events must be consistent; one preceding another.
2. Strength of the association of the events to one another.
3. Consistency with existing knowledge. Clinical, pathologic, and other knowledge of the disease in question, and knowledge of other pathologic effects of the supposed causal factor, leading to a judgment as to whether or not a causal hypothesis is reasonable.

Having now defined, albeit too incompletely, what epidemiology is, we can return to the title of "epidemiology of late effects of radiation in man." A first event is now well identified; it is ionizing radiation from whatever source man may be exposed. The sequential event, the effect, is much less well defined, in fact one may say it is virtually undefined. Fortunately, however, we do have some knowledge, which permits the development of the hypothesis, that there are late effects of radiation in man. It is the results of testing this hypothesis that forms the basis of the remainder of my remarks.

Before going on, and because I feel that it may be appropriate to keep in mind, since epidemiology relies heavily upon statistical methods, I should like to quote something once said by W. V. Mayneord:

> ". . . part of the pleasurable impact of numerical data may arise from the power of a number to obscure uncomfortable uncertainty as to what we are talking about."

I do not intend to present you with masses of numerical data. These are available to you for you to evaluate as you will.

The late effects of man's exposure to ionizing radiation are probably twofold. One effect is upon the genetics of man—the other is upon man as an existing whole animal, the somatic effect.

Genetic effects, as late effects of irradiation in man, are extremely difficult to evaluate in the populations available to study. Indeed if the hypothesis of geneticists (*2*) is carried to its ultimate conclusion, all of us present here represent an example of late effects of irradiation as it has affected the genetic pool since the beginning of life and will continue to affect it with perhaps increasing rapidity as man's environment accumulates increasing amounts of irradiation to which man must inevitably be exposed.

An effect ascribed to radiation, which may lie somewhere in the area of either genetic or somatic effects, is the finding of chromosomal abnormalities following exposure to various sources of radiation. It is not my intention to explore this field of cytogenetics here. Perhaps the state of knowledge concerning this interesting and valuable contribution may best be summarized by quoting Lisco and Conard (*3*) in a recent article. "The biological significance of persistant chromosome aberrations in blood lymphocytes of hematologically normal persons many years after exposure to ionizing radiation is not known. In particular, any role that aberrations of this type may play in the pathogenesis of radiation-induced leukemia can only be surmised at present. It is problematical and indeed doubtful whether chromosome aberrations in lymphocytes can serve to indicate abnormalities in other tissues, except perhaps inferentially."

Now, if I may, I will confine the remainder of my remarks to studies of somatic effects of ionizing radiation in man. Most of the ascribed effects may be listed in a brief manner as follows:

1. Increased rate of carcinogenesis.
2. Accelerated aging.
3. An increased rate of congenital or fetal abnormalities.
4. Cataract formation.

Other less well-defined somatic effects have been suggested by several investigators and include such things as:

1. Autoimmune reactions with such manifestations as amyloidosis.
2. Inflammatory disease states, such as nephritis, pneumonitis, and possibly thyroiditis.

Some of the less well-defined somatic effects may indeed be simple manifestations of the premature or accelerated aging process as may most somatic effects.

Effects of radiation are dependent on some rather obvious factors. Exposure to a single organ or tissue will manifest an effect, if one exists, primarily in that organ or tissue. Whole-body radiation may produce many concurrent tissue effects, which will be a symptom complex not easily or readily identified except in acute exposure incidents.

Certain organs or tissues, simply by virtue of anatomical placement or physiological activity, are more susceptible to effects of radiation. Good examples are skin, lens of the eye, thyroid gland and bone.

Factors of dose, whether fractionated or single dose, play an important role in evaluation of potential effects. While it is generally accepted that radiation dose exposure is cumulative, it is also generally accepted that between exposures some repair of cells and tissues occurs dependent upon the extent of injury. The amount of time allowed for repair may be an important factor when there is a fractionation of dose. The more time perhaps the greater the repair and the lessened probability of an identifiable effect.

Perhaps a comment made in 1960 by Dr. Austin Brues in testimony before the Joint Atomic Energy Committee of the United States Congress (*4*) demonstrates in words the almost impossible complexity of the problems of identifying late radiation effects. "The present unanswerability of these questions lies in the fact that they ask, in addition to empirical data, for a basic understanding of the aging process and of the common denominator, or denominators, of the carcinogenic equation, which we simply do not have and must develop techniques and modes of thought to answer."

After considering all of the pitfalls and precautions necessary let us examine now, in more detail, what has been described as late somatic effects in man as a result of exposure to ionizing radiation.

In the investigations of a carcinogenic effect of radiation several reports in the scientific literature present virtually irrefutable evidence that bone sarcomas in radium dial painters may result fom exposure to radium (*5, 6*), thyroid cancers may result from exposure to x rays (*7, 8*), lung cancer may result from exposure to radon daughters present in uranium mine atmospheres (*9, 10*), skin cancer may result from exposure to x rays (*11*), leukemia may result from exposure to a variety of sources of radiation (*12*), and liver tumors may result from exposure to thorium present in the contrast medium, Thorotrast (*13*). All of these reports refer to carcinogenic effects described in man.

The process of accelerated aging and its associated manifestations have not been specifically identified in man with the possible exception of cataract development. The best population available for study of aging effects from exposure to radiation is that under study by the Atomic Bomb Casualty Commission in Hiroshima and Nagasaki, Japan. So far, accelerated aging has not been specifically identified in this population (*14*). Indeed the problem becomes very complex from the simple fact that, as yet, the parameters necessary to identify the process of aging are either not defined or are so ill defined as to lead to a confusion of results.

If one looks to animal experimentation one can find that reports of a "speeding up" of the aging process are confined to measurements of a limited sphere of effects. In a recent publication of the proceedings of a colloquium on Radiation and Aging we find that R. R. Kohn (*15*) in summarizing much of the discussion states that the "discussion centered on the evidence for the general applicability of collagen deposition as a main determinant for age-related changes. . . . There was a divergence of opinion as to whether exposure to radiation caused an increased laying down of collagen as a direct effect, or was secondary to initial post-irradiation damage to the tissues leading to interference with the blood supply." Others at this same conference made reference to autoimmune reactions, changes in endocrine physiology, and so on. While several most interesting and excellent experiments were reported there still remains the prime difficulty of identification of aging effects and specifically ascribing these effects to the agent of ionizing radiation.

One single thought seems to emerge from all I have said so far: The present state of our knowledge concerning late effects of radiation in man is, to say the least, somewhat vague and poorly documented. A few studies, such as those of radium dial painters, of thymic irradiation, of leukemia following x ray or atomic bomb exposure, and of uranium miners, are outstanding for their positive findings relating cause and effect.

Examples taken from studies currently in progress carried on by the National Center for Radiological Health of the U.S. Public Health Service give some further insight to the kinds of information about somatic radiation effects, or lack of effects, which we believe to be extremely valuable in the overall evaluation of the problem of late effects in man.

The Cooperative Thyrotoxicosis Therapy Follow-up Study, still continuing, was begun in 1961 to test for an increase in leukemia incidence in patients receiving therapeutic doses of radioiodine for hyperthyroidism over the rate observed in hyperthyroid patients treated by other means. The preliminary results of this study will be reported in full by Drs. Saenger and Thomas, and Mrs. Tompkins (*16*) this fall, but at the risk of slight "scooping" of their report I will say only that no difference in leukemia incidence rates for these two groups of patients has been demonstrated. Of possible interest, however, is that the total group of patients treated with both surgery and radioactive iodine do have a higher incidence of leukemia than any other group. This study has involved 36,000 patients from 24 medical centers from which there is now available a current health status on over 96 percent of the study population.

Another study that is still in progress concerns possible low-level radiation effects in thyroid glands of the young. In this instance a community reported to have been subject to high exposure from radioactive fallout was studied in comparison to a similar community not exposed to fallout. The study is designed to test whether there is an increase in thyroid neoplasms among children who were exposed as compared to children who were not exposed. So far, the results of this study are not conclusive but would indicate that there is no difference in the overall pattern of thyroid disease among the two groups.

A corollary study to the one just described concerns an analysis of "Surgically Treated Thyroid Disease Among Young People in Utah" (*17*). Again the preliminary results are not conclusive but in this instance somewhat suggestive of an increased incidence of thyroid cancer and other thyroid disease during the past 5-year period. Whether this is a true increase and whether it is significant on the basis of radiation exposure are questions yet to be answered.

Still another study currently underway and hopefully reaching a conclusive end soon, concerns itself with the possible risk of leukemia associated with radiation exposure in utero or immediately postnatal (*18*). Again preliminary results are suggestive and titillating, but by no means conclusive nor significant to the degree that all the various factors of cause and effect with the added evaluation of demographic characterization of the population being studied are clear cut. The significance of this study, if any, awaits final analysis.

Studies have been done concerning associations of mongolism to radiation exposure with a strong suggestive cause and effect (*19*).

Studies have been done and results again are suggestive concerning relationship of radiation and increased fetal abnormalities and stillbirths (*20*).

Many other studies are either underway or in the early planning stages. All these studies are geared to identification, if possible, of specific somatic effects, in the human population, which can be identified as caused by radiation. If cause and effect can be identified specifically and then dose of radiation also specified, we will begin to have some knowledge concerning the magnitude of the risk our human population faces from many potential exposure situations.

In conclusion I admit to asking more questions than giving answers to questions. The present state of our knowledge concerning specifically identifiable late effects of irradiation in man is, to say the least, somewhat vague and very sketchily documented. Most studies conducted upon human populations have had either negative or equivocal results. A few studies are outstanding for their positive findings. It would be extremely presumptuous to state that our knowledge of late effects of radiation in man has progressed tremendously over the past several years. We are really in a very early stage of our investigations and hopefully not merely guessing or falling into the trap of extrapolation of animal experiments to man. We are in the beginning stages of removing fears, phobias, and mysteries by accumulating the facts concerning this ubiquitous agent of ionizing radiation and its effects upon mankind.

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RADIATION ACCIDENTS

George E. Thoma, Jr.

The types of radiation accidents that have occurred in the field of nuclear technology since its formal beginning in 1945 will be reviewed and discussed. Any discussion of these accidents should be prefaced by calling attention to the fact that the safety record in the industry is remarkable. This is true not only in relation to the extremely small number of incidents resulting in irradiation to personnel, but also to the extremely low incidence of nonirradiation accidents. In this latter category the incidence rate is less than one-third of the National Safety Council rate for all industries.

A few definitions are essential. A radiation accident is defined as an unforeseen occurrence involving exposure to ionizing radiation either externally from a source not in contact with the body or from contamination on or within the body from radionuclides. By nuclear technology is meant any industrial activities in which nuclear energy plays a role, whether primary or secondary; thus, the small plant that uses a radioactive thickness gauge would be included as well as the large Atomic Energy Commission installation with its great complex of radioactive processes and sources. A minor accident is defined as one in which the exposure of the individual exceeds currently recommended maximum levels but is not of sufficient quantity to result in detectable clinical symptoms. A major accident is defined as one in which the exposed individual develops clinical symptomatology attributable to radiation overexposure.

Source of Radiation Exposure

There are two major categories of sources of accidental exposure to humans by radiation. The source of radiation may be external to the body so that the radiation reaches the individual and is absorbed depending on its physical characteristics. The principal sources of external radiation are x-ray generators, particle accelerators, sealed sources of radionuclides, and reactors. From these the radiation may be beta, gamma, or neutron, and in the case of particle accelerators may also be other particles such as deuterons and mesons.

The other principal category of sources of exposure is by surface or internal contamination with radionuclides. These radionuclides may be deposited on the skin, enter the body through ingestion, inhalation, or contaminated wounds. Both external irradiation and radionuclide contamination can, and often do, occur simultaneously.

Minor Accidents

In reviewing the relative frequency of the various factors in the production of minor radiation accidents it is evident that although every effort is made to make equipment foolproof, it is impossible to overcome the element of human failure. Two main features recur repeatedly on reviewing the details of minor accidents. The first is the failure of individuals to know of the presence or to appreciate the hazards of radiation. The other is the malfunctioning of protection arrangements in the known presence of radiation.

Since by definition minor accidents do not result in any detectable clinical findings the diagnosis of external irradiation is limited to the history of exposure or the results of dosimetry devices. Management is limited to observation, advice concerning the avoidance of further exposure, and reassurance.

In the case of irradiation through contamination, the diagnosis is dependent on measurements of the surface of the skin with radiation monitors, or the internal burden with whole- or partial-body counters, and the radioassay of excreta, secretions, and/or removed tissue.

In the management of contamination accidents the prompt removal of all radioactive material from the person of the individual is the task of special interest to both the physician and the health physicist. External decontamination of the skin is accomplished by scrubbing the intact skin with appropriate complexing, cleaning, or other agents that are not harmful in themselves. It is important to avoid harsh procedures that would introduce surface contamination into the body through the skin. In handling contaminated wounds, the general surgical principles apply. The main modification is in debridement. Here it is important to avoid introducing skin contamination into the wound. It may be necessary to use a small-block dissection for penetrating wounds, which would not ordinarily be treated in this manner.

When the level of internally deposited radionuclides is excessive, it is recommended that every effort be made to reduce the body burden through means appropriate to the specific radionuclide present, for example, chelating agents may be used to enhance the removal of radionuclides. Tri-sodium calcium diethylenetetraamine pentacetic acid (DTPA) is effective in the removal of plutonium, yttrium, uranium, and mixed fission products.

Major Accidents

The major radiation accidents are of three main types: Experimental assembly accidents; reactor accidents; and production facility accidents. In general the first type has involved acceptance of inadequacies in safety design to facilitate experimental procedures. The reactor accidents usually have been the result of unapproved deviations from routine procedures. The production facility incidences generally have occurred because of the presence of unanticipated conditions, which made previously adequate controls of fission material ineffective.

Regardless of the nature of the exposure situation, the general clinical syndrome associated with a large external whole-body dose of ionizing radiation is characteristic and is termed the acute radiation syndrome. The general pattern is divided into a set of prodromal symptoms, and then following a latent period of variable length, a subsequent period of manifest illness. The manifest illness may be differentiated into a primarily hematologic disorder, a gastrointestinal syndrome, and a fulminating series of central nervous system phenomena.

The only procedures necessary to determine the clinical severity of the injury are clinical observations of the patient and routine hematologic laboratory tests. The physical measurement of the exposure dose is a helpful supplementary piece of information but not absolutely essential to the management of the patient. The variations in human response to radiation are such that, given an accurate measurement of the dose, one would still be unable to predict the degree of resulting injury within a wide range.

In the therapy of these patients good medical management, firmly based on an understanding of the pathophysiology of the acute radiation syndrome, does not differ from the treatment of less modern maladies. The development of bone marrow transplantation has provided a possible specific therapeutic procedure but should be reserved for those cases in whom clinical and laboratory evidence of severe radiation injury suggest a high probability of a fatal outcome.

INDUSTRIAL EXPOSURE TO RADIATION

John C. Villforth and *Richard F. Boggs*

One of the first commercial uses of radiation was the application of radium and mesothorium luminous compounds to aircraft instruments and military markers during World War I. In the 1930's, industrial radiography and gas well-logging became accepted industrial techniques, but their use was not accelerated until World War II; however, not until the Atomic Energy Act of 1946, which encouraged the peaceful uses of atomic energy, were the industrial aspects of radiation fully realized.

With the encouragement of the Atomic Energy Commission, new applications of radioactive materials were investigated and the production of radioisotopes increased rapidly. The development of nuclear reactors made the production of many new radioisotopes possible. Byproduct materials, produced in a reactor, are under the regulatory control of the Atomic Energy Commission, or in more recent years "agreement States." To date, 17 States, which include about 50 percent of the Nation's population, have entered into agreement with the Atomic Energy Commission. These States have, in general, also stepped up their control of other forms of ionizing radiation, such as radium and industrial use of x rays.

The early unknown biological effects of radiation provided the incentive for the AEC to develop the most effective specialized injury-prevention program that American industry has ever devised. As a result, only seven fatalities directly related to nuclear radiation exposure occurred in AEC-owned facilities through 1964. During the period 1943–64, involving over 388 million man-days of possible exposure at these facilities, only 20,124 man-days were lost from radiation exposure (including 18,000 days charged to three fatalities) in contrast to 989,462 man-days from all other causes.

The Bureau of Labor Statistics report of March 1966 shows 132,000 people employed in atomic energy work, of which about 101,000 are employed in AEC-owned facilities. The remaining 31,000 were employed in privately owned facilities. The people reported as directly employed in atomic energy work are working in areas where there is full cognizance of the potential health hazard from radiation, and in which they are under the surveillance of a radiation safety program. These factors are responsible for the enviable safety record.

In addition to the group reported as "atomic energy worker," there is another large group of potentially occupationally exposed people not under the regulatory control of the AEC that use x rays, particle accelerators, neutron generators, or radium as tools or as a byproduct to some other operation; for example, the uses of x-ray diffraction, flash x rays, industrial x radiography, well-logging, and neutron activation are increasing as more effective, lower cost equipment is being made commercially available. Examples of potential radiation exposure to a "nonoccupationally exposed" technician from unnecessary radiation are the x-ray emission from certain high-voltage tubes used in the electronic industry, and the contamination found in facilities that repair aircraft instruments containing luminous compounds of radium.

Since these applications involve sources of radiation not under the control of any Federal agency, and only recently under the regulatory control of the agreement States, information on the extent of the potential problem from these areas is not well defined. In the past, there has been no requirement for the users to report incidents, accidents, or over exposures. More important, unless the user is in an agreement State or one of the other States that operate a radiation protection program, he will not have the benefit of the surveillance of his procedures. Defects in equipment or faulty techniques may not be identified and corrected.

Results extrapolated from information obtained from the States during 1966 indicate that approximately 10,000 industrial x-ray units are in use in the United States. Only 5,200 of these have been inspected by regulatory agencies, and of those inspected about one quarter were found not in compliance with State radiation regulations.

Information obtained in 1965 from manufacturers of particle accelerators indicates that there are about 150 neutron generators, 300 Van de Graaffs, and 150 particle accelerators of other types in operation in the United States. These units can present a public and occupational health problem because of the widespread use of these relatively inexpensive machines for activation analysis in research and industrial quality control procedures. High levels of radiation exposure can occur from x ray and neutron production, tritium environmental contamination, and induced radioactivity.

During the past 5 years, nearly 8,000 low-voltage x-ray tubes have been sold in the United States. It is estimated that 80 percent of these are being used in x-ray diffraction units, the operators of which have a very limited knowledge of the hazards associated with the operation of these units.

Radium is used in about 1,800 industrial facilities for such applications as well-logging, gauging static elimination, and radiography. Improper storage and handling, and the absence of leak testing are frequent observations.

The number of shops that repair instruments containing radium luminous compounds is not well known, although there are 324 aircraft instrument repair facilities approved by the Federal Aviation Agency. Limited surveys of these facilities by State health agencies have indicated radium contamination well above levels accepted in the atomic industry. The contamination appears to be a result of cleaning and stripping the instruments, rather than from the dial painting.

It is apparent that, in addition to the very effective radiation control program and the enviable radiation safety record of the atomic energy industry, a large group of workers are exposed to radiation incidental to their primary occupation. This group has not had the benefit of a radiation control program. Every effort must be made by radiological health agencies and standards groups to see that these workers have the same benefit of protection as the atomic energy worker.

ENVIRONMENTAL CONTAMINATION FROM ATOMIC PLANTS

Collin A. Mawson

When I first became acquainted with the waste disposal problem, so-called, it was a problem because of ignorance. We did not know much about the disposal of radioactive wastes; therefore we were very cautious. We were highly conservative in all the calculations and assumptions that we made because we simply did not know. During subsequent years, we have learned a lot about the things we were ignorant about in the early 1950's. Yet, we find ourselves bound very often by the assumptions and the doubts of the early days, and we do not seem to adapt ourselves very quickly to the knowledge accumulated in all those years.

In the early 1950's there was an atmosphere of alarm and despondency about the waste disposal problem. On the radio and in the newspapers there were pronouncements by the pundits, even the responsible ones, to the effect that the waste disposal problem might be so serious that it would limit, or perhaps even prevent, the multiplication of nuclear power stations.

In Canada in the early 1950's we had come to a decision on the general direction of our policy. We were faced in the late 1940's and early 1950's with a choice between the development of the production of isotopes on a very large scale from the processing of nuclear fuel, or the production of a viable nuclear power industry. Canada is a small country in population although not in size, and we realized that we could not afford to do both. In the early 1950's we had developed excellent processing procedures and we also thought we had a good power program. We chose the power program so it behooved us to face the waste disposal problem as well.

Waste Management Experiments

We had the advantage at Chalk River of a very large area all around the reactors—about 10,000 acres. It is a wild area of forest and rocky ground. There are eight or nine lakes on the property. There is a very large river, the Ottawa River; in fact, we have nearly everything except mountains and sea. We were in a very good position to do experimental work in this field because we were far from any built-up area. The first water intake ~~on~~ the Ottawa River is about 15 miles downstream. The average flowrate of the river is about 10^{10} gallons per day. It is a large river, a mile and a quarter across and flows about 6 miles a day.

Looking to the future, we realized that from the economic point of view it was very important that we should develop waste disposal systems applicable to nuclear power stations situated near to, or even inside, a large city. For that reason, the waste disposal systems at Chalk River were devised so that they would be safe in the immediate neighborhood of a large center of population.

As the program developed it became apparent that we were not going to be involved in Canada in the high-level waste disposal problem from processing plants, because with the heavy-water type of reactor the fuel is not reprocessed.

Therefore we did not accumulate vast quantities of high-level wastes in stainless steel tanks which were, in fact, sitting right on the bank of the Ottawa River. One of my worries when I took over the waste management system was what might happen if one of these high-level tanks leaked into the ground. The only way to answer that question, as far as I could see, was to carry out experiments in the field.

Fixation in Glass

We had some wastes and we knew that other people were going to be in trouble with high-level wastes so the chemical engineers devised a fixation system that would be adequate for dealing with high-level wastes. The wastes were fixed by fusion into a nepheline syenite glass, and they carried out laboratory leaching tests on small samples of glass; however, we did not know whether the results of leaching would be the same in the field. So again the only way to find out was to try.

The engineers prepared 25 glass blocks that contained 1,500 curies of mixed fission products, of which 440 curies were strontium 90 with about the same amount of cesium 137, and we buried them in a swamp, 4 feet below the ground water level. This was done in 1960, and we have been following the results very carefully ever since.

To get leaching, we had to use the worst kind of glass we could produce, and this was done by loading it with corrosion products and uranium. It turned out that when this glass was first buried the amount of radioactive material that came out of it was almost exactly what was forecast from the laboratory leaching tests for high-quality glass. By 1963, after 3 years, the leaching rate had been reduced to one-tenth of what the laboratory tests said it might be. By 1966 it had been reduced to one-fiftieth of this figure. When we made our annual survey this spring we found that from the 440 curies of strontium 90 in the glass only 0.10 per microcurie per day is being leached out into the ground water.

The leaching rate is essentially the rate at which the glass is dissolving into the ground water. The reason for the difference in leaching rate between laboratory and field results is that the ground water had been running for miles through sand, so it is a pretty strong solution of silica. When it comes up against a piece of glass, it doesn't really dissolve it at all because it is saturated with silica already, and only an exchange process is going on.

The total amount of radioactivity that has come out of this glass disposal, made in 1960, is still less than 10 millicuries.

So many of these fixation processes have been successfully tested that there seems to be no real high-level waste "problem" at all. There are half-a-dozen different ceramics, glasses, and other fixation products, and I, personally, would be quite happy to see such glasses and ceramics buried in the ground; in fact, from what we have been able to see, the leaching rate is so low that you might almost throw them into a river. If you put so much activity into the blocks of glass that they would melt, putting them into the sea or into a large body of water would be a good thing if you wanted to keep them cool.

I have never been able to understand why it is necessary to prevent melting. If the glass is in the ground and it melts, it also melts the ground around it and produces resistant material all around that is practically uncontaminated. It is so hot that the water nearby is turned into steam before it reaches the glass. As the radioactivity decays the glass cools and the water penetrates into the active mass, but by this time much of the radioactivity is no longer there.

Low-Level Wastes

The low-level wastes are usually much more difficult to handle than the high-level wastes because they are in very large volume. We had some experience with dissolved "waste" after the 1952 accident to the NRX reactor, and the lessons learned helped us in deciding on operating policy for low-level aqueous wastes. The cooling water, running over the damaged fuel, collected in the basement. We ended up with a million gallons of water in the basement containing 10,000 curies of mixed fission products, of which about 1,000 curies were strontium 90 and another 1,000 of cesium 137. The active water was pumped by pipeline into trenches cut in the sand of the waste disposal area. The trenches were backfilled with sand, and sampling wells were installed so that we could watch any movement of contaminated ground water.

After 2 years of weathering most of the activity was still within about 2 feet from the bottom of the trenches. After 13 years the extreme edge of the leached material in the ground water, which is about 14 feet below the surface, is only 250 feet away from the place where it was deposited. Most of it is still within 6 feet of the bottom of the trenches.

This made us feel that we could dispose of our main low-level wastes by putting them into the ground. The liquid low-level wastes are mainly the water in which we store our spent fuel for the first 6 to 12 months for "cooling." The fuel is stored in large water-filled concrete trenches. The water becomes contaminated from induced activity on the fuel sheaths and from occasional ruptured fuel elements. There is a constant bleed-off of water to keep the level of contamination low. At first this replacement rate was about 50 gallons a minute. Now it is only about 5 gallons a minute because it is purified by ion exchange. For disposal we made a large hole in the ground, which we filled with rock, and the water was pumped into this pit.

Up to the present time about 14,000 curies of mixed fisson products have entered the pit and very nearly all of this material remains near the bottom of the pit in spite of continual leaching—the extreme edge of the subsurface "plume" has moved less than 600 feet. Some has reached the surface in a swamp near to the waste disposal area, but the level of contamination of surface waters is not a significant health hazard.

Ground Disposal of Higher Level Wastes

With this experience we decided to find out what would happen if a high-level waste tank leaked by setting up a major field experiment. We did two experiments, in 1954 and 1955, which I shall treat as a single experiment. We had nearly 13,000 gallons of medium-level active waste that was about 2.5 M in nitric acid and part of it also contained 0.5 M ammonium nitrate. The mixed fisson product content was more than 1,000 curies, including 360 curies of strontium 90, 320 curies of cesium 137 and 120 curies of ruthenium 106.

We made pits in the ground and pumped the waste in over the course of 3 or 4 days, and we have been following the results ever since. This may sound like a very rash experiment, but we had done a commonsense calculation. The Ottawa River runs at an average rate of 10^{10} gallons per day (18,500 cubic feet per second) and if the whole disposal percolated through the ground and entered the river over the course of 6 months (a highly unlikely event), there would be no public health problem provided it was diluted into one-tenth of the volume of the river. We felt we were not being irresponsible in carrying out the experiment.

You will realize from the composition of the waste that it was quite dense. The acid solution sank quickly to the water table and moved at the velocity of the ground water, which in that particular place is about 1 foot per day. The radioactive material behaved differently. Much of it was removed by the soil on the way down to the water table, but part of the ruthenium ran with the ground water. The strontium 90 moved at about one-fiftieth of the velocity of the ground water. The cesium ran considerably more slowly than that. It was 4 years before we saw any movement of cerium or antimony and we have not yet (after 13–14 years) been able to detect any movement of the other fisson products.

The acid was neutralized by the ion exchange capacity of the soil, which in our case is very low because it is plain sand. It is only 1 milliequivalent per 100 grams; however, there is a lot of sand, so by the time the acid had moved through the ground water about 40 years, there was no detectable acid left. After that point the dissolved radionuclides behaved as they do in solution in water.

I am not going to describe in detail the movement of the radionuclides under the ground because the results have been published by P. J. Parsons (*2*). Every year we carry out a drilling program to outline the tip of the tongue of radioactivity that is moving outward. We take samples across the track and in depth and we can calculate the total amount of radioactivity in each slice of this tongue, thereby obtaining a year-to-year record of its underground movement.

Chalk River is a research station that can be expected to produce a relatively large amount of radioactive wastes, but the total amount of radioactivity that entered the Ottawa River from CRNL last year was only 7 percent of the total amount of radioactivity that was coming down the river anyway as bomb fallout. We have a small nuclear power station, NPD, just upstream from the town where CRNL people live and we are happy to know that the amount of waste produced is so small that the concentration is undetectable in the river water a few hundred yards from the outfall. The regulations governing discharge of radioactive wastes to the environment often limit the concentration in the outfall to the maximum permissible concentration in drinking water or, in the case of stack gases, to the maximum permissible concentration in air. This is sometimes unnecessarily restrictive, but it shows that the discharges from power stations have to be very small.

Nuclear Accidents

We must now ask—what happens in the case of an accident? The ground rules for considering this problem are written down in a document that we refer to as WASH-740. This deals with the problem of how many people might be killed in a really large power station accident, and the number of people that might be injured. It is a horrifying document, but the accidents dealt with are what we call "Maximum Credible Accidents." It is interesting to see how these Maximum Credible Accidents are conceived.

We are able to forecast from our knowledge of the rate and direction of movement of the ground water that we shall never have a waste disposal problem from these large depositions in the ground. There is a lake about 700 feet away from the waste disposal area and we know how the wastes are going to move from the waste disposal area to the lake. It would take 150 years for the first strontium atom to get from the disposal area into this lake. This is 5 half-lives of strontium 90. The strontium will be distributed over the whole of the track, so very little strontium 90 will ever reach the open water.

We have come to the conclusion that, provided one has experimental evidence of how radionuclides react with the soil and knows the rate and direction of movement of water under the soil, there is no real "problem." The ground is a very safe container for radioactive wastes if you know how the wastes will behave in the ground.

Wastes from Nuclear Power Stations

Wastes from nuclear power stations are of a very different nature in more than one sense; the composition of the waste is different because instead of fission products the activity is mainly corrosion products. The other thing is that it is very difficult to forecast where radioactive wastes are going to come from in a power station. In a fuel reprocessing plant or in an experimental research institution such as Chalk River, the sources of waste are obvious. The number of failed fuel elements that can be economically tolerated in a power station is very small. Our power stations are refueled on power, so failed fuel is normally removed. The control laboratories produce broken glassware and some active solutions. The personnel showers, laundry, and decontamination center produce a certain amount of liquid waste, and there is "garbage," such as used rubber gloves and other protective clothing. The solid wastes are comparatively low level. The liquid wastes are also in this category, and when you realize that thermal power stations are usually situated near large bodies of water with very high dilution capabilities the "problem" during normal operation is not a serious one.

Great efforts are made to think of the worst possible thing that could happen: for example, you have a 10-inch stainless steel pipe carrying steam, and to produce the Maximum Credible Accident, as specified for the reactor, you have to assume that this steam main is fully opened up. Nobody has ever seen a large steam main that was burst in this way. They always crack and the crack runs down the pipe. But you cannot produce the Maximum Credible Accident by having a cracked steam main like that; you have to assume that it is torn apart. You also assume that the accident happens at the worst possible time when weather conditions are at their very worst. You have a reactor which has a control system and a separate safety system. You assume that the control system breaks down and that the safety system breaks down at the same time. The Maximum Credible Accident does not happen unless all these unlikely events occur simultaneously. To me an accident of that kind is not a credible accident; it is an incredible accident.

Consideration of the effects of the Maximum Credible Accident is an interesting psychological process because at the beginning everybody knows perfectly well that this accident is never going to happen (probability is 10^{-6} to 10^{-9} per annum). Yet, as the discussion proceeds, this subtly becomes more and more credible until before very long everybody around the table is assuming that it is going to happen! I believe that what we ought to be looking at is not Maximum Credible Accidents that are never going to happen; we should be spending our time looking at all the ordinary everyday little accidents that are going to happen.

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CHANGES INDUCED BY THE IRRADIATION OF NUTRITIONAL ELEMENTS

Roger Ghys

At present, ionizing radiations are used on a large scale to sterilize or otherwise improve the keeping properties of a number of products intended for human consumption.

Large-scale investigations, started some 10 years ago and sponsored among others by the U.S. Army, have shown that no grossly toxic substance was produced by the irradiation of foodstuff; doses adequate in most instances, for either radiosterilization or radioprotection, have been determined. For a technique for the preservation of nutrients to be acceptable, however, it is not enough to demonstrate the absence of toxic compounds. Many other post-irradiation changes, some of which are not yet fully know, can influence the wholesomeness or acceptability of foodstuffs. On the other hand, the very large variations in the radiosensitivity of microorganisms responsible for the deterioration of many products makes a complete standardization of irradiation techniques difficult and, in our opinion, illogical. This may explain why the expansion of the commercial use of ionizing radiations has been much slower than anticipated.

In this field many experiments are done under circumstances not unlike those of the researches on the effect of cigarette smoke sponsored by the tobacco industry or the preclinical trials of the ill-fated thalidomide. Instead of simply looking for facts, they are designed to try to prove a thesis: The wholesomeness of irradiated nutrients; general metabolic changes are sometimes studied in depth, but the side effects on other systems can in many experiments easily escape the investigator. Also there is often little basis for extrapolating to the human conclusions of experiments done in unrelated species.

A wide range of doses can be used for the preservation of nutrients. About 10 kilorads will destroy the germinative power of many seeds.

A typical application is the cobalt 60 gamma irradiation of potatoes to inhibit sprouting. Slightly higher doses will prevent the maturation of insect larvae and of animal parasites. The "LD 90" for most bacteria is in the order of 100 kilorads, but can be much higher in anaerobic conditions; viruses will be inactivated by a few megarads; however, the radiosensitivity of microorganisms is very dependent on the medium in which they are irradiated. We have also recently shown, for several bacteria and viruses, that the inactivation curve is sometimes very different from the classical exponential. Small doses can have a stimulating effect, in other cases, there is a marked tailing of the inactivation curve, making absolute sterilization impossible in practice.

The dose that will "kill" the virus will also inactivate many enzymatic systems; thereby retarding or completely inhibiting autolysis of most products. In many cases, however, real sterilization is not necessary. All that is needed is the reduction of viable bacterial counts below a certain level. This "radiopasteurization" can often be achieved with a dose of a few hundred kilorads, and it will considerably increase the storage life of many foodstuffs. The main advantage of radiosterilization is that it can be done at room temperature (or even at a much lower temperature). If the product has been sealed (preferably under vaccum) before the irradiation, in an envelope that will prevent any further contamination, it will then keep for several months at room temperature and practically indefinitely at refrigerator temperature above freezing.

Irradiation can also induce a number of changes in the product itself.

The radioactivation of processed foods is of great concern to the layman, although those more familiar with nuclear physics know that it is practically impossible with ionizing radiations of an energy less than 4 MeV. Meneely has shown in 1964 that no significant radioisotope production takes place below 12 MeV in meats.

Another possibility is the production of free radicals in irradiated products. Nineteen parts per million (dry weight basis) manganese (+2) have been found in strawberries irradiated with 200 kilorads at 0° C., but the wholesomeness of these strawberries does not seem to be affected by the presence of manganese (+2) free radicals.

The nutritional value of irradiated foods can be influenced by radiochemical effects. As early as 1949, Goldblith and Proctor were able to demonstrate that riboflavin and carotene in solution were destroyed by 0.66 Mrep and they demonstrated that this was an "indirect effect" of the radiation. Other compounds are fairly sensitive to radiations; those of nutritional importance are thiamine, vitamin B_6 (pyridoxin), niacine, riboflavin, and, above all, vitamin K. Various amino acids have also been reported destroyed, but others are extremely radioresistant. Destruction of vitamins A and E can also occur. Animal fats undergo complex changes that generally diminish their digestibility; nevertheless, the changes after radiosterilizing doses are in general not sufficiently extensive to cause any severe loss in the nutritional value of thse macronutrients, and occasional beneficial effects have been observed—the reduction of the antigenicity of milk proteins (Kraybill et al., 1959).

For human consumption, organoleptic properties are all important. A nutrient can be wholesome and digestible. It will probably not be accepted if it has an unusual taste, flavor, or even color. Organoleptic changes are generally not objectionable after a "pasteurizing" dose of radiation but they can be very pronounced after a sterilizing dose; for example, irradiated beef tastes like liver and will not be accepted by most people.

The most important but most difficult problems, from an anthropocentric viewpoint, are the changes induced by the feeding of irradiated nutrients. Although several hundred papers and reports have been published, opinions are still divided. Most of the work has been done in rats and dogs. Only radiation doses were chosen fairly empirically, and the control dogs were sometimes fed very strange and nutritionally inadequate diets. A number of detrimental effects have been observed: carcinogenicity, reduced growth rate, reduced life span, lowered reproduction performances, muscular dystrophy (in rats), decreased levels of alklaine phosphate and monoamineoxydase in various organs. In 1960 Monsen also reported a high frequency of heart lesions in Cb mice who were fed irradiated food, but this observation has not been confirmed since. However, these changes are very inconsistent and the difference between animals fed irradiated and nonirradiated food is often less than the strain or sex difference; sometimes animals fed irradiated foods have a better growth curve than the controls.

On the whole, the statement of the Surgeon General's Office "that foods irradiated up to absorbed doses of 5.6 Mrads with a cobalt-60 source of gamma radiation . . . have been found to be wholesome" can be accepted without much reservation. Nevertheless, we think that the best possible irradiation techniques to insure the least detrimental biochemical alterations in foodstuffs and their perfect acceptability have still to be established. Also the "selective sterilization" of vaccine by well-chosen doses of radiation should be developed in the near future.

Ingeniously chosen microbiological systems could probably advantageously replace higher animals for the testing of biochemical alterations in irradiated nutrients; for instance, a nonvirulent strain of tubercle bacilli will grow well on a purely synthetic medium where the only sources of carbon are glycerol and L-aspargine. It can be used to test changes caused by the irradiation in these compounds. On the other hand, organoleptic changes can only be tested with the help of human subjects.

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